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February 28, 2002

MEMORANDUM

SUBJECT: **Propanil**. Human Health Risk Assessment (Revised)

PC Code 028201
Case No. 0226
DP Barcode: D281147

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The following (revised) human health risk assessment has been prepared by the Health Effects Division for Phase One of the reregistration process for propanil. Propanil risk assessment is based on the following supporting memoranda:

Propanil. Product Chemistry Chapter for the Reregistration Eligibility Decision. (K. Dockter memo, 9/19/01).

Propanil. Report of the Hazard Identification Assessment Review Committee (Y.G. Yang and S.L. Makris memo, 8/15/01).

Propanil. Report of the Cancer Assessment Review Committee (S. Diwan memo, 6/19/01).

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Propanil. Report of the FQPA Safety Factor Committee (B. Tarplee memo, 9/19/01).

Propanil. The Outcome of the HED Metabolism Assessment Review Committee (S. Kinard memo, 8/31/01).

Propanil. Revised Residue Chemistry Chapter for the Reregistration Eligibility Decision (S. Kinard memo, 2/28/02).

Propanil. Revised Chronic Dietary Exposure Assessment (S. Kinard memo, 2/28/02).

Tier 1 Drinking Water Estimated Environmental Concentrations for Propanil and its Major Degradate 3,4-Dichloroaniline (3,4-DCA) from use on Rice (I. Abdel-Saheb memo, 9/14/01).

Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision (RED) Document for Propanil (1st Revision), (S. Recore memo, 2/8/02).

Propanil. Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document (S. Makris memo, 10/30/01).

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1.0 SUMMARY

Propanil is a selective postemergence herbicide registered for use on rice, barley, oats, and wheat to control broadleaf and grass weeds. Propanil is also registered (but not currently marketed) for turf use at commercial sod farms. Usage on rice accounts for approximately ninety-nine percent of total U.S. (annual average) usage of 9,370,000 pounds active ingredient (a.i.) per year. Propanil is available as an emulsifiable concentrate (EC), a liquid or dry flowable (DF), a low volume (LV), and ultra low (ULV) formulation and is typically applied as a broadcast treatment by ground and aerial equipment. Propanil belongs to the acetanilide class of pesticides and, acting primarily in the leaves, is a strong inhibitor of the *Hill reaction,* disrupting normal photosynthesis.

The toxicological database for propanil is considered minimally adequate for hazard characterization. The studies submitted to support guideline requirements are supplemented by relevant open literature publications.

In general, propanil has low acute toxicity (although primary eye irritation is observed in rabbits). The principal toxic effect of propanil is methemoglobinemia and hemolytic anemia, which is seen in different species, in studies of varying lengths of time. Methemoglobinemia results in the development of hemolytic anemia with decreases in hemoglobin, red blood cell (RBC) count, and packed cell volume. Other than slightly decreased fetal body weights (with or without accompanying delays in skeletal ossification) there was no apparent adverse effect of *in utero* propanil exposure on the morphological development of the fetuses in the prenatal developmental toxicity studies in rats and rabbits. Effects observed in the two generation reproduction study in rats (delayed vaginal perforation, delayed balanopreputial separation, and decreased mean sperm count) are highly suggestive of neuroendocrine disruption. Also, there is evidence in the peer-reviewed literature that propanil has immunotoxic potential.

The HED Hazard Identification Assessment Review Committee (HIARC) met on July, 19, 2001 to select the studies, endpoints, and dose levels (NOAEL/LOAEL) for human risk assessment. No appropriate endpoint attributed to a single dose was identified. An acute RfD was not established. The propanil chronic Reference Dose (RfD) is 0.03 mg/kg body weight/day based on the LOAEL (9.0 mg/kg/day) of the chronic toxicity/carcinogenicity study in rats. The endpoint of concern is methemoglobinemia and the uncertainty factor (UF) is 300 based on 10x for interspecies extrapolation, 10x for intra-species variability, and 3x for the use of a LOAEL.

Risk assessment for short/intermediate-term incidental oral exposure, short/intermediate/long-term dermal exposure, and short/intermediate/long-term inhalation exposure are all based on the LOAEL (9.0 mg/kg/day) of the chronic

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toxicity/carcinogenicity study in rats, with an uncertainty factor of 300. Based on a comparison of oral and dermal toxicity studies in rabbits, an (upper-bound) estimate of 20% has been calculated for dermal absorption. A 100% absorption rate was applied to inhalation exposure.

The HED Cancer Peer Review Committee has classified propanil into the category termed *"Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential".* A quantitative carcinogenic dose-response assessment (Q_1* approach) is not indicated for propanil.

The Food Quality Protection Act (FQPA) Safety Factor Committee concluded that the FQPA safety factor be retained at 10x for the following weight-of-evidence considerations; 1) there is qualitative evidence of increased susceptibility following pre- and postnatal exposure to propanil in the 2-generation reproduction study in rats; 2) a developmental neurotoxicity study with propanil is now required due to suggestive evidence of neurotoxicity including neuropathological lesions (sciatic nerve degeneration) seen in the rat chronic toxicity/carcinogenicity study; and 3) evidence consistent with neuro-endocrine disruption seen in the two-generation reproduction study in rats and the rat chronic toxicity/carcinogenicity study. This evidence is supported by the structure activity relationship (SAR) consideration for linuron, which has a known neuro-endocrine mode of action.

The HED Metabolism Assessment Review Committee (MARC) has reviewed the propanil toxicology and metabolism data (meeting dates of 1/16/96 and 8/7/01) and concluded that human health risk assessment should be based on estimates of exposure to propanil (parent), 3,4-dichloroaniline, and related residues convertible to 3,4-dichloroaniline (3,4-DCA).

No appropriate effects attributed to a single exposure (dose) was identified in the rat or rabbit developmental toxicity study. The prenatal developmental toxicity studies were examined for possible endpoints that should be used in acute dietary risk assessment for the general population or for females aged 13-50. In the rat developmental toxicity study, body weight loss was observed in dams at 100 mg/kg/day after only 4 gavage doses of propanil and a similar effect was noted in the rabbit developmental toxicity study in which body weight loss was observed in does following 6 daily gavage doses at 100 mg/kg/day. However, there was insufficient evidence that these findings were the result of a single dose. No hazard was identified and quantitative *acute risk assessment is not required.* However, the HIARC has recommended that a study be conducted to examine the onset of methemoglobinemia following oral administration of propanil in the rat; this study would include blood measures on day 1 after initiation of treatment and could provide information for use in acute risk assessment scenarios.

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A refined (tier 3) chronic dietary risk assessment was conducted. Human dietary exposure was determined, considering the level of propanil residue in/on food commodities and their potential consumption by multiple population subgroups. Dietary risk estimates were then calculated by comparing dietary exposure to the chronic population adjusted dose (cPAD), which is the reference dose divided by the additional FQPA safety factor of 10. "Anticipated" residue estimates were determined based on field trial studies and estimates (weighted average percentage) of the percentage of rice and small grain crops treated with propanil. Food consumption data (3-day mean) were from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII),1989-1992. Dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM™), which incorporates residue and consumption data to calculate risk as a percentage of the cPAD. Estimated chronic dietary risk estimates for all population subgroups are less than the propanil cPAD (0.003 mg/kg/day) and do not indicate a concern for this route of exposure. The most highly exposed population subgroup is "all infants < 1 year of age" with an estimated exposure corresponding to 13% of the cPAD.

Monitoring data for propanil residues in ground and surface water are available but not adequate to develop estimated environmental concentrations (EECs) for the aggregate dietary (food and water) risk assessment. Instead, models have been used to estimate surface and groundwater concentrations expected from normal agricultural use. These model estimates were compared to human drinking water levels of comparison (DWLOCs), the theoretical concentration of a pesticide in drinking water that would be an upper limit (determined as 100% of the cPAD) in light of the aggregate exposure to that pesticide from food sources (no residential exposure to propanil is expected). The drinking water EEC for groundwater (0.35 ug/L) is below the DWLOC for all population subgroups. The surface water EECs (a range of 6 to 72 ug/L) are below the DWLOC for all population subgroups except for children at the upper-bound EEC of 72 ug/L.

HED did not complete a cumulative risk assessment as part of this reregistration review for propanil because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with propanil.

There is a potential for exposure to propanil during mixing, loading and application activities, or when guiding aerial applications (flaggers). All these activities are collectively referred to as "handler" tasks. Five general scenarios were considered representative of the range of handler activities, crops, or acres treated and equipment used. The scenario-specific risk estimates for short- and intermediate-term *dermal* exposure and short- and intermediate-term *inhalation* exposure were calculated and then added together to obtain overall risk estimates at increasing levels of personal protection. A margin of exposure (MOE) estimate is the ratio of exposure to a

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determined dose level (in this case 9.0 mg/kg/day). Based on the HIARC-determined uncertainty factor of 300 for this dose/endpoint, the Agency considers a MOE of 300 to be adequately protective for both short- and intermediate-term propanil exposure.

Risk estimates were calculated assuming increasing levels of personal protection equipment, ranging from a baseline of typical work clothing (long-sleeved shirt and long pants, no respiratory protection and no chemical-resistant gloves) to engineering controls such as a closed cab or a closed loading system. Generally, most occupational handler scenarios had combined (dermal and inhalation) MOE estimates that meet or exceed 300 at some level of personal protection. In some cases though, engineering controls, such as closed loading systems or closed cab tractors, are needed. The scenarios with the highest associated risks have high daily chemical use based on application rates and/or high acreage treated.

MOEs that meet or exceed the "target" MOE of 300 at the baseline level are the following; 1) mixing/loading dry flowable for groundboom application to small grains; 2) applying sprays, using a groundboom, to rice at 80 acres per day, and to small grains at 80 and 200 acres per day; and 3) flagging for spray applications on small grains.

MOEs that meet or exceed the target MOE of 300 at the minimum PPE level are the following; 1) mixing/loading liquids for aerial application to small grains at 350 acres per day; 2) mixing/loading liquids for groundboom application to rice at 80 acres per day, and to small grains at 80, and 200 acres per day; and 3) applying sprays, using a groundboom, to sod farms at 80 acres per day.

MOEs that meet or exceed the target MOE of 300 at the engineering control level are the following; 1) mixing/loading liquids for groundboom application to sod farms at 80 acres per day; 2) applying sprays by aerial equipment to small grains at 350 and 1,200 acres per day; 3) applying sprays, using a groundboom, to rice at 200 acres per day; and 4) flagging for spray application to rice and sod farms.

Calculations of risk based on dermal and inhalation exposure indicate that the combined MOEs are less than the target MOE of 300 with maximum risk reduction measures for the following exposure scenarios: 1) mixing/loading liquids for aerial application to rice at 350, 1200, and 3200 acres at 6 lbs a.i./acre, mixing/loading liquids for aerial application to rice at 1200 and 3200 acres at 3 lbs a.i./acre, 2) mixing/loading liquids for aerial application to small grains at 1200 acres at 1.14 lbs a.i./acre, 3) mixing/loading liquids for aerial application to turf at 350 acres at 10 lbs a.i./acre, 4) mixing/loading liquids for groundboom application to rice at 200 acres at 6 lbs a.i./acre, 5) mixing/loading dry flowable for aerial application to rice at 3200 acres at 6 lbs a.i./acre, 6) mixing/loading dry flowable for aerial application to rice at 3200 acres at 3 lbs ai/acre, 7) applying sprays, using aerial application to rice at 350, 1200, and 3200 acres at 6 lbs a.i./acre, and 8) applying sprays, using aerial application to turf at 350

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acres at 10 lbs a.i./acre.

Workers can be exposed to propanil residue when entering previously treated areas to perform various activities such as scouting and irrigating. Current labeling requires a 24 hour Restricted Entry Interval (REI), i.e., workers cannot enter treated areas for 24 hours postapplication to perform routine hand labor activities. The estimated MOE for scouting rice (following application at the maximum rate) is greater than the target MOE of 300 one day *after* application with minimal foliage development (based on early season use). The estimated MOE for scouting rice (at the typical application rate) is greater than the target MOE of 300 *on* the day of application with minimal foliage development (based on early season use).

The estimated MOE for scouting small grains (at the maximum application rate) is greater than the target MOE of 300 *on* the day of application with minimal foliage development (based on early season use). The estimated MOE for low-exposure activities such as mowing and scouting turf is greater than the target MOE of 300 *on* the day of application. However, the estimated MOE for high-exposure turf activities such as harvesting and transplanting does not meet the target MOE of 300 until 18 days following application.

HED has determined that, other than the possibility of spray drift exposure, there are no potential post-application residential or recreational exposures. The turf use is restricted to sod farms only. Although propanil treated sod may eventually be used in residential settings (i.e., residential lawns), propanil residues are not expected to occur at levels that would present a residential post-application risk concern.

The database for propanil is considered minimally adequate for risk assessment, data deficiencies have been identified. Studies required by the Agency include: 1) developmental neurotoxicity; 2) 28-day inhalation toxicity; 3) 30-day oral study in rats with methemoglobin measurements at days 1, 5, 7, 14, 21, and 30; and 4) a guideline immunotoxicity study (or a literature search to better characterize its immunotoxic potential.

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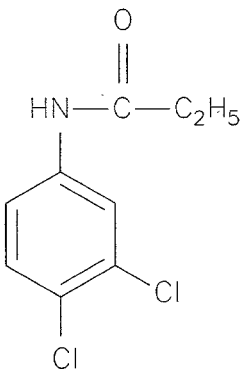
2.0 PHYSICAL / CHEMICAL PROPERTIES CHARACTERIZATION

Chemical Structure:



CAS NT-1 Systematic Chemical Name: N-(3,4-dichlorophenyl)propanamide.

CASRN: 707-98-8

Chemical Class: Anilide

Common Name: propanil [BSI, ISO, & WSSA]

Other Names: 3',4'-dichloropropionanilide [IUPAC]

Empirical Formula: C9H9CL2NO

Molecular Weight: 218.1

Physical State: dark grey crystal

Melting Point: 87-89° C

Vapor Pressure: 2.6 x 10^{-7} mbar

Octanol/Water Partition Coefficient: P_{ow} = 193

Water Solubility: 0.13 g/L at 20° C

Stability: stable; active ingredient hydrolyzes in strong acid or base

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3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Table 1. Acute Toxicity of Propanil, Technical

Guideline No.	Study Type	Results	Toxicity Category
81-1	Acute Oral (Rat)	LD_{50} = 1080 mg/kg	III
81-2	Acute Dermal (Rabbit)	LD_{50} > 2000 mg/kg	IV
81-3	Acute Inhalation (Rat) STAM 80G (78.3% a.i.)	LC_{50} = 6.1 mg/L	IV
81-4	Primary Eye Irritation	Iritis, conjunctivitis present in all rabbits, cleared by day 14; corneal opacity cleared by 4 days	II
81-5	Primary Skin Irritation	Slightly irritating P.I.I. = 0.2/4.0	IV
81-6	Dermal Sensitization	Negative	N/A
81-8	Acute Neurotoxicity	Not required	

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Table 2. Toxicity Profile

Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
SUBCHRONIC TOXICITY STUDIES		
870.3100 90-Day oral toxicity rodents (Wistar rat)	MRID 00015459, 00046259 (1961) 0, 0.01, 0.033, 0.10, 1.0, 5.0 % (diet) (0, 10, 33, 100, 1000, 5000 mg/kg/d)	NOAEL = 33 mg/kg/day LOAEL = 100 mg/kg/day based on increased relative spleen weight in females and decreased hemoglobin in males.
870.3100 90-Day oral toxicity rodents (CD-1 mouse)	MRID 40402901 (1983) 0, 25, 200, 1600, 12800 ppm (diet) (M: 0, 6.6, 49, 442, 5325 mg/kg/d) (F: 0, 9.6, 78, 566, 6467 mg/kg/d)	NOAEL = 6.6/9.6 (M/F) mg/kg/day LOAEL = 49/78 (M/F) mg/kg/day based on histopathological findings in the liver (hepatocytic pleomorphism and hepatocytic multifocal necrosis).
870.3200 21-Day dermal toxicity (NZW rabbit)	MRID 41777001, 41961800 (1990) 0, 250, 500, 1000 mg/kg/d 6 hrs/day; 5 days/week	NOAEL = 250 mg/kg/day LOAEL = 500 mg/kg/day based on decreased body weight gain (day 20) and decreased food consumption (days 14-20).
DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES		
870.3700a Prenatal developmental toxicity in rodents	MRID 00058588 (1980) 0, 0.8, 4.0, 20, 100 mg/kg/d Gavage; GD 6-15	Maternal NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight gain during treatment. Developmental NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae.
870.3700b Prenatal developmental toxicity in nonrodents (NZW rabbit)	MRID 00058589 (1980) 0, 4, 20, 100 mg/kg/d Gavage; GD 6-18	Maternal NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on mortality, clinical signs of toxicity, and weight loss during treatment. Developmental NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on slightly decreased mean fetal weight.

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Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
870.3800 Reproduction and fertility effects (SD rats, 2-generations)	MRID 44604301 (1998) 0, 60, 150, 600 ppm (diet) (F0 M: 0, 4, 11, 43 mg/kg/d) (F0 F: 0, 5, 13, 51 mg/kg/d)	**Parental/Systemic** NOAEL = 11/13 (M/F) mg/kg/day LOAEL = 43/51 (M/F) mg/kg/day based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. **Reproductive** NOAEL = 11/13 (M/F) mg/kg/day LOAEL = 43/51 (M/F) mg/kg/day based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and decreased mean testicular sperm count and production rate in F1 adult males. **Offspring** NOAEL = 11/13 (M/F) mg/kg/day LOAEL = 43/51 (M/F) mg/kg/day based on reduced F1 and F2 pup weights, delayed vaginal perforation and balanopreputial separation in F1 adolescents, and organ weight changes in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in males and females).
CHRONIC TOXICITY AND CARCINOGENICITY STUDIES		
870.4100a Chronic toxicity rodents	See 870.4300, Combined chronic toxicity/carcinogenicity	
870.4100b Chronic toxicity dogs (beagles, 1-yr)	MRID 42962901 (1993) 0, 200, 1600, 2300 ppm (diet) (M: 0, 5, 45, 79 mg/kg/d) (F: 0, 6, 42, 85 mg/kg/d)	NOAEL = < 5/6 (M/F) mg/kg/day LOAEL = 5/6 (M/F) mg/kg/day based on macrocytic, regenerative, methemoglobinemia (decreased erythrocytes, hemoglobin, hematocrit, and mean cellular hemoglobin concentration; increased mean cell volume, methemoglobin, and reticulocytes.; increased Heinz bodies in females at week 51), and endogenous pigment (hemosiderin) in the kidney of both sexes and the liver of males
870.4200 Carcinogenicity (CD-1 mice; 104-wk)	MRID 43391701 (1994) 0, 500, 1000 ppm (diet) (M: 0, 74.9, 150 mg/kg/d) (F: 0, 88.6, 174.1 mg/kg/d)	NOAEL = < 74.9/88.6 (M/F) mg/kg/day LOAEL = 74.9/88.6 (M/F) mg/kg/day based on methemoglobinemia (increased methemoglobin and Heinz bodies in males) and blue discoloration of the extremities. Evidence of carcinogenicity: malignant lymphomas in females at 174.1 mg/kg/d

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Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
870.4300 Combined chronic toxicity/carcino-genicity (SD rat; 104-wk)	MRID 43303201 (1994) 0, 200, 600, 1800 ppm (diet) (M: 0, 9.0, 27.7, 88 mg/kg/d) (F: 0, 11.5, 38.3, 145 mg/kg/d)	NOAEL = < 9.0/11.5 (M/F) mg/kg/day LOAEL = 9.0/11.5 (M/F) mg/kg/day based on clinical chemistry findings in both sexes (increased methemoglobin at weeks 13, 26, and 52; decreased packed cell volume and red blood cells at weeks 26and 52), increased spleen weight in females at 52 weeks, and gross- and histo-pathological findings at 104 weeks (enlarged spleen in females, small seminal vesicles and prostate in males, hemosiderosis in spleen of males, brown pigment [probably hemosiderin] in proximal convoluted tubules of females and endometrial polyps in females). Evidence of carcinogenicity: testicular interstitial cell adenomas in males at 27.7 and 88 mg/kg/d.
MUTAGENICITY STUDIES		
Gene Mutation 870.5100 Bacterial reverse gene mutation assay	MRID 00155085 (1980)	Propanil was **negative** in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and in *Escherichia coli* WP2 up to cytotoxic doses (≥1,000 µg/plate +/-S9) in independent trials.
Gene Mutation 870.5100 Bacterial reverse gene mutation assay	MRID 00028625 (1979)	Independent trials were **negative** in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 up to cytotoxic doses (≥1,000 µg/plate +/-S9) and in *Escherichia coli* WP2 up to the highest dose tested (1,000 µg/plate +/-S9).
Gene Mutation 870.5300 *In vitro* mammalian cell gene mutation test	MRID 00155084 (1984)	In a Chinese Hamster Ovary (CHO)/HGPRT cell forward gene mutation assay, independent tests were **negative** up to cytotoxic doses without S9 activation (125 µg/mL) and with S9 activation (175 µg/mL).

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Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
Cytogenetics 870.5385 Mammalian bone marrow chromosome aberration test	MRID 00155083 (1983)	An *in vivo* bone marrow cytogenetic assay was **negative** in CD-1 male mice administered 0, 26.5, 106, or 265 mg/kg/day by oral gavage once or once daily for 5 consecutive days. Doses selected for this study represented 1/4, 1/10 or 1/40 of the acute LD_{50}, respectively. Overt toxicity was manifested as decreased spontaneous motor activity, lethargy and piloerection in animals receiving ≥106 mg/kg/day in both dosing regimens. No data were provided to support the claim of decreased metaphases in the high dose animals, and this deficiency compromised the acceptability of the study. However, since there was a clear indication of toxicity to the test animals, and no differences in LOAELs between male and female mice were seen in the subchronic or chronic studies, the doses should be considered adequate.
Other Genotoxicity 870.5500 Bacterial DNT damage or repair tests	MRID 00028625 (1979)	Propanil was **negative** for differential cytotoxicity in *Escherichia coli* strains W3110/p3478 (pol A +/-) up to an equivalent cytotoxic dose (5 µg - S9) but was **positive** for the induction of preferential inhibition of repair-deficient *Bacillus subtilis* M45 (rec-) at 0.01-5 µg without S9: S9 activation was not included in this study.
Other Genotoxicity 870.5575 Mitotic gene conversion in *Saccharomyces cerevisiae*	MRID 00028625 (1979)	In a D3 mitotic recombination assay, propanil was **negative** for the induction of mitotic recombinants at doses up to 0.1 % with or without S9 mix. Independent trials were performed.
Other Genotoxicity 870.5550 Unscheduled DNA synthesis in mammalian cells in culture	MRID 00028625 (1979)	In an unscheduled DNA synthesis assay in WI-38 human fibroblasts, propanil was **negative** up to an insoluble level (1000 µg/mL).

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Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
METABOLISM STUDIES		
870.7485 Metabolism and pharmacokinetics (SD rat)	MRID 41796400, 41796402 **(1991)** A: single oral low dose (2.5 mg/kg) B: multiple oral low dose (2.5 mg/kg for 15 days) C: single oral high dose (300 mg/kg) D: intravenous dose (0.7 mg/kg in saline)	The majority of the radioactivity (78-90%) was excreted in the urine, and 2-13% was excreted in the feces. Most of the radioactivity was eliminated within 24 hours for all except the high oral dose where it took 48 hours to eliminate 90%. For the i.v. data, females excreted 10% in the feces, while males excreted 2%. The carcass contained 0.18-0.71% of the radioactivity, with the liver having the highest residue. Of the total of 13 metabolites identified, three major metabolites accounted for 17-44% of the radioactivity and were involved in hydroxylation and oxidation of the propanamide moiety. Other metabolites included 3,4 dichloroaniline, and its N-hydroxy and 6-hydroxy derivatives, which are associated with methemoglobin formation.

3.1.1 Hazard Characterization

The toxicological database for propanil is considered minimally adequate for hazard characterization. The studies submitted to support guideline requirements are supplemented by relevant open literature publications.

The data base for acute toxicity for the purpose of product labeling and preliminary toxicity assessment is considered complete. No additional screening acute toxicity studies are required at this time. As evaluated in the standard acute screening study battery, propanil has low acute toxicity, with toxicity categories of III (oral) and IV (dermal, inhalation, and primary skin irritation); no dermal sensitization was observed, however, primary eye irritation was observed in rabbits (toxicity category II).

The acute oral systemic toxicity of propanil has not been adequately characterized for the purposes of risk assessment. The HIARC has recommended that a study be conducted to examine the onset of methemoglobinemia following oral administration of propanil in the rat; this study would include blood measures on day 1 after initiation of treatment and could provide information for use in acute risk assessment scenarios.

For non-acute exposures, administration of propanil to different species for varying lengths of time leads characteristically to the development of

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methemoglobinemia. The resulting methemoglobinemia causes the development of hemolytic anemia, which is characterized by decreases in some or all of the following parameters: hemoglobin, RBC count, and packed cell volume. Hematological and histopathological evaluations also revealed Heinz bodies in RBCs and hemosiderin deposits in the spleen and kidneys.

Subchronic dietary administration of propanil in rodents and dogs resulted in findings consistent with methemoglobinemia and hemolytic anemia. In rats, this included decreased hemoglobin and increased spleen weight at doses of 100 mg/kg/day and higher. In the mouse, cyanosis of the ears and skin, decreased erythrocyte counts, increased liver and spleen weights, and histopathological lesions of the liver and spleen were observed. In the liver, these histopathological findings included incidences of hepatic pleomorphism, multifocal necrosis, nuclear variation, and pigmented Kupffer cells at higher doses, and treatment-related incidences of hepatocytic pleomorphism and/or hepatocytic multifocal necrosis at the LOAEL of 49 mg/kg/day. In the spleen, there was an increase in the severity of the grade of lesions (hemosiderin and extramedullary hematopoiesis) observed at higher doses. Following 21 days of consecutive dermal applications in New Zealand white rabbits, decreased body weight gain and food consumption were observed at 500 mg/kg/day; however, there were no observed treatment-related alterations in hematological or organ parameters that were consistent with methemoglobinemia. The HIARC recommended that several studies be conducted to further characterize the toxicity of propanil following short or intermediate-term exposures. These include a 28-day inhalation study and a 30-day oral study in rats that includes methemoglobin measurements at days 1, 5, 7, 14, 21, and 30. Additionally, due to evidence in the published literature suggesting that propanil is a potential immunotoxic chemical, the HIARC recommended that the Registrant conduct a guideline immunotoxicity study or submit a literature search to better characterize its immunotoxic potential.

Other than slightly decreased fetal body weights (with or without accompanying delays in skeletal ossification), there was no apparent effect of *in utero* propanil exposure on the morphological development of the fetuses in the prenatal developmental toxicity studies in rats and rabbits. In the two-generation reproduction study in rats, delayed vaginal perforation and balanopreputial separation was observed in F1 adolescents, and decreased mean testicular sperm count and production rate was noted in F1 adult males. These findings are highly suggestive of neuroendocrine disruption, although hormonal measurements in the two-generation reproduction study did not identify specific alterations in testosterone, luteinizing hormone (LH), or estradiol levels in F0 males at study termination. Nevertheless, the delays in sexual development are supported by a number of other considerations, including: the presence of treatment-related testicular interstitial cell tumors in the rat chronic/oncogenicity study with propanil (often related to neuroendocrine disruptions), and the similarities between the reproductive toxicity profiles of propanil to linuron and flutamide, two structurally-

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related chemicals with a demonstrated neuroendocrine mode of action affecting the hypothalamic-pituitary-testicular (HPT) axis. The HIARC judged that the evidence consistent with neuroendocrine disruption in the 2-generation reproduction study was indicative of qualitative susceptibility of the offspring.

In the most recent (acceptable) chronic toxicity assessments with propanil, long-term dietary exposure resulted in evidence of treatment-related methemoglobinemia in rats and dogs; NOAELs were not identified in either species. In the chronic toxicity/carcinogenicity study in Sprague-Dawley rats, this evidence consisted of increased methemoglobin levels, decreased packed cell volume and red blood cells, and enlarged spleens at the lowest dose tested; additional hematological findings, with increased severity, were observed at higher dose levels. Histopathological findings (brown pigment in hepatic Kupffer cells and in the proximal convoluted tubules of the kidney) were also presumed to be related to the methemoglobinemia. Evidence of hepatic toxicity included centrilobular liver cell enlargement and hepatic granulomatous inflammation. Kidney toxicity was demonstrated by increases in blood urea nitrogen (BUN). Unrelated to the methemoglobinemia in this study, toxicity to the reproductive system included hypoplastic prostate and seminal vesicle, epididymal aspermia, and interstitial cell adenomas of the testes in males, and endometrial polyps, mammary galactocoeles, dilated uteri, and cystic ovaries in females. These findings are consistent with the neuroendocrine etiology described above. Other observed toxicity to the nervous system consisted of axonal degeneration of the sciatic nerve at the highest dose tested. In beagle dogs, macrocytic, regenerative methemoglobinemia was observed as decreased levels of red blood cells (RBCs), hemoglobin, hematocrit, and mean cell hemoglobin concentration (MCHC) and increased levels of mean cell volume (MCV), methemoglobin, and reticulocytes. Hemosiderin deposition was observed in the bone marrow, kidney, and liver. Kidney toxicity was evidenced by increases in BUN, creatinine, and potassium, and hepatic toxicity was evidenced by increased absolute and relative liver weights.

A developmental neurotoxicity study is required for propanil, based upon evidence of neurotoxicity in the data base, consisting of neuropathological lesions (axonal degeneration of the sciatic nerve) in the rat chronic toxicity/carcinogenicity study and evidence consistent with neuroendocrine disruption in the two-generation rat reproduction study (delayed sexual maturation) and the rat chronic toxicity/carcinogenicity study (Leydig cell tumors).

In a battery of acceptable mutagenicity assays, propanil was not found to be genotoxic. Propanil was not mutagenic in bacteria or in cultured mammalian cells. There was also no indication of a clastogenic effect up to toxic doses *in vivo*. Propanil did, however, cause DNA damage in a DNA repair-deficient strain of *B. subtilis* but not in the pol A^- strain of *E. coli*. The relevance, therefore, of this positive result in *B. subtilis* is unclear, since DNA damage was not manifested as point mutations in

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microbial systems or mammalian cells, mitotic recombinations in yeast, DNA damage in mammalian cells or chromosomal aberrations in whole animals.

In an evaluation of the carcinogenic potential of propanil, an increased incidence of testicular interstitial (Leydig) cell adenomas was observed in Sprague-Dawley rats following 2 years of exposure and was attributed to treatment. Hepatocellular adenomas in female Sprague-Dawley rats in the same study were attributed to excessive toxicity, and were not considered to be relevant to the evaluation of the carcinogenic potential of propanil. Additionally, evidence of a treatment-related increase in commonly-occurring malignant lymphomas in female CD-1 mice following 18 months of propanil exposure was considered to have a limited impact on the overall conclusion regarding the weight-of-the-evidence for the carcinogenic potential of propanil. Based upon these findings and the lack of genotoxicity in a battery of assays, propanil was classified into the category of *"Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential."*

In a metabolism study in rats, the majority of propanil and its metabolites were excreted in the urine within 24 hours, with only 2-13% excreted in the feces and minimal retention in the carcass or internal organs. Of the total of 13 metabolites identified, three major metabolites accounted for 17-44% of the radioactivity and were involved in hydroxylation and oxidation of the propanamide moiety. Other metabolites included 3, 4-dichloroaniline (DCA), and its N-hydroxy and 6-hydroxy derivatives which have been associated with methemoglobin formation in open literature studies.

Propanil has been reported to be contaminated (at a low level) with the cytochrome P450 enzyme inducers 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), which are structural analogs of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). A summary of short-term bioassays compiled by the National Toxicology Program (NTP) states that "3,3'-4,4'-tetrachloroazobenzene caused typical dioxin-like effects, such as thymic atrophy, an increase in liver weights, induction of hepatic cytochrome P4501A, and decreased mean body weight gains. Furthermore, in the 13-week studies, a sharp decrease in circulating thyroxine concentrations was observed even at the lowest dose (0.1 mg/kg) tested in rats. Other effects included a decrease in epididymal spermatozoal concentration in mice, major effects on the hematopoietic system, and increased incidences of hyperplasia of the forestomach in 3 and 30 mg/kg males and 30 mg/kg females. A no-observable-adverse-effect-level (NOAEL) was not reached in rats. The NOAEL in mice was 0.1 mg/kg. Comparison of various dioxin-like effects in these studies with those reported in the literature indicate that 3,3',4,4'-tetrachloroazobenzene is six to two orders of magnitude less potent than 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." (TOX-65, 1998)

Chronic toxicity/carcinogenicity studies are not available for TCAB or for TCAOB. The *specific* endpoint(s) and related dose levels that may be observed in chronic toxicity

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studies, or the *specific* carcinogenic potential of these compounds is not known. However, since TCAB and TCAOB have been present in all toxicological test materials, including test material for the chronic toxicity/carcinogenicity studies cited above, the Agency believes that propanil risk (*including carcinogenic potential)* has not been underestimated.

3.2 FQPA Considerations

3.2.1 Database Summary Relative to FQPA

Developmental toxicity studies in rats:	Acceptable study available.
Developmental toxicity studies in rabbits:	Acceptable study available.
Two-generation reproduction study in rats:	Acceptable study available.
Developmental neurotoxicity study:	Not available. (Required).
Acute and subchronic neurotoxicity studies:	Not available. (Not required).
Acute delayed neurotoxicity study in hen:	Not required.

3.2.2 Evidence of Quantitative / Qualitative Susceptibility

Acceptable guideline studies are available for the assessment of prenatal developmental toxicity in rats and rabbits and for the assessment of reproductive toxicity in rats (following two generations of exposure to propanil). There was *no* evidence of age-related quantitative susceptibility in the submitted developmental and reproduction studies. Other than slightly decreased fetal body weights (with or without accompanying delays in skeletal ossification) there was no apparent effect of *in utero* propanil exposure on the morphological development of the fetuses in the prenatal developmental toxicity studies in rats and rabbits. In the two-generation reproduction study in rats, delayed vaginal perforation and balanopreputial separation was observed in F1 adolescents, and decreased mean testicular sperm count and production rate was noted in F1 adult males. These findings are highly suggestive of neuroendocrine disruption, although hormonal measurements in the two-generation reproduction study did not identify specific alterations in testosterone, luteinizing hormone (LH), or estrodiol levels in F0 males at study termination.

Nevertheless, the delays in sexual development are supported by a number of other considerations, including: the presence of treatment-related testicular interstitial cell tumors in the rat chronic/oncogenicity study with propanil (often related to neuroendocrine disruptions), and the similarities between the reproductive toxicity profile of propanil to linuron and flutamide, two structurally-related chemicals with a demonstrated neuro-endocrine mode of action affecting the hypothalamic-pituitary-testicular (HPT) axis. [In rat studies, linuron has been shown to; 1) delay sexual maturation; 2) cause abnormalities in male reproductive organs and result in alterations to spermatogenesis; and 3) result in significant incidences of Leydig cell tumors after

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prolonged exposure].

Neither the acute nor the subchronic neurotoxicity study in adult rats with propanil has been submitted to the Agency. However, there was evidence suggestive of neurotoxicity in the propanil data base. The findings included; 1) neuropathological lesions (sciatic nerve degeneration) in a rat chronic toxicity/carcinogenicity study and 2) evidence consistent with neuro-endocrine disruption (delayed vaginal opening and preputial separation) in the two-generation reproduction study in rats, and in the rat chronic toxicity/carcinogenicity study (increased incidence of testicular interstitial cell tumors); this evidence is supported by SAR considerations (the known neuro-endocrine mode of action of linuron, which is structurally related to propanil). Based upon these considerations, a developmental neurotoxicity study in rats for propanil is required but has not been submitted to the Agency.

Although no mechanistic studies have been submitted to the agency, open literature publications addressed the mode of action of propanil in regard to inducing methemoglobinemia. The mode of action for methemoglobinemia involves the oxidation of hemoglobin to form methemoglobin. It is known that the very young (less than 3 months of age) and the elderly are at greater risk for developing methemoglobinemia. Death from methemoglobinemia is rare but usually occurs when the methemoglobin level exceeds 70%, especially in infants and young children.

Literature searches have been conducted and no additional neurotoxicity, developmental or reproductive toxicity was found.

3.2.3 Findings of the FQPA Safety Factor Committee

The Health Effects Division (HED) FQPA Safety Factor Committee met on September 10, 2001 to evaluate the hazard and exposure data for propanil. Based on the evidence outlined above, the OPP FQPA Safety Factor Committee concluded (9/10/01) that the 10x safety factor (10x more protective than the Reference Dose) should be retained for assessing propanil dietary (food) and aggregate (food and water) risk.

3.2.4 Rationale for FQPA Safety Factor Finding

The FQPA Safety Factor Committee concluded that the FQPA safety factor be retained at 10x for the following weight-of-evidence considerations; 1) there is qualitative evidence of increased susceptibility following pre- and postnatal exposure to propanil in the 2-generation reproduction study in rats; 2) a developmental neurotoxicity study with propanil is required due to suggestive evidence of neurotoxicity in the data base including neuropathological lesions (sciatic nerve degeneration) in a rat chronic toxicity/ carcinogenicity study; and 3) there is also evidence consistent with neuro-endocrine

disruption in the two-generation reproduction study in rats and in the rat chronic toxicity/carcinogenicity study. This evidence is supported by the structure activity relationship (SAR) consideration that linuron, which is structurally related to propanil, has a known neuro-endocrine mode of action.

3.3 Dose-Response Assessment

Table 3. Summary of Toxicology Endpoint Selection

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	No appropriate endpoint attributed to a single dose was identified. An acute RfD was not established.		
Chronic Dietary	LOAEL = 9.0 UF = 300	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostate in males.	Chronic toxicity/ carcinogenicity study in rats
		Chronic RfD = 0.03 mg/kg/day	
Cancer	Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential.	(1) Propanil induced testicular interstitial cell adenomas in male rats. The hepatocellular adenomas in female rats occurred only at an excessively toxic dose. The increase in commonly occurring malignant lymphomas in female mice added little to the overall weight of evidence for the carcinogenic potential of propanil. (2) Propanil was not mutagenic.	Carcinogenicity study in rats and mice
Incidental Oral; short- and Intermediate-Term	LOAEL= 9.0 UF = 300	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostate in males.	Chronic toxicity/ carcinogenicity study in rats
Dermal; Short-Intermediate-Term[a]	LOAEL= 9.0 UF = 300	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostate in males.	Chronic toxicity/ carcinogenicity study in rats
Dermal; Long-Term[a]	LOAEL= 9.0 UF = 300	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostate in males.	Chronic toxicity/ carcinogenicity study in rats
Inhalation; Short-, Intermediate-Term[b]	LOAEL= 9.0 UF = 300	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostate in males.	Chronic toxicity/ carcinogenicity study in rats
Inhalation; Long-Term[b]	LOAEL = 9.0 UF = 300	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostate in males.	Chronic toxicity/ carcinogenicity study in rats

a An oral endpoint was used for dermal exposure: dermal absorption factor of 20% of oral exposure shall be used.

b An oral endpoint was used for inhalation exposure: inhalation exposure assumed equivalent to oral exposure; a 100% absorption rate is applied.

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3.3.1 Endpoint Selection Discussion

Dietary Exposure - Acute Reference Dose: No appropriate effects attributed to a single exposure (dose) were identified in the rat or rabbit developmental toxicity study. The prenatal developmental toxicity studies were examined for possible endpoints that should be used in acute dietary risk assessment for the general population or for females aged 13-50. In the rat developmental toxicity study, body weight loss was observed in dams at 100 mg/kg/day after only 4 gavage doses of propanil and a similar effect was noted in the rabbit developmental toxicity study in which body weight loss was observed in does following 6 daily gavage doses at 100 mg/kg/day. However, there was insufficient evidence that these findings were the result of a single dose. No hazard was identified and quantitative acute risk assessment is currently not required. However, the HIARC has recommended that a study be conducted to examine the onset of methemoglobinemia following oral administration of propanil in the rat; this study would include blood measures on day 1 after initiation of treatment and could provide information for use in acute risk assessment scenarios.

Dietary Exposure - Chronic Reference Dose: For non-acute exposures, administration of propanil to different species for varying lengths of time leads characteristically to the development of methemoglobinemia. Methemoglobinemia results in the development of hemolytic anemia, which is associated by decreases in some or all of the following parameters: hemoglobin, RBC count and packed cell volume.

In the chronic toxicity/carcinogenicity study in rats, the following treatment-related effects were observed: 1) statistically significantly increased (33-45% above control levels) methemoglobin at weeks 13, 26, and 52; 2) significantly decreased (4-6%) packed cell volume and red blood cells at weeks 26 and 52; 3) significantly increased absolute weight of spleen (14%) in females at 52 weeks; 4) enlarged spleens in 104 week necropsied females; 5) small seminal vesicles and prostates in 104 week necropsied males; 6) hemosiderosis in spleen of males; 7) brown pigment (probably hemosiderin) in proximal convoluted tubules of females; and 8) an 8% incidence of endometrial polyps in females (compared to 4% in controls). A NOAEL was not established in this study for systemic effects due to the findings at 200 ppm (LDT). An uncertainty factor (UF) of 100 is applied to account for both interspecies extrapolation and intra-species variability. An additional UF of 3 is applied for the use of a LOAEL (total UF = 300).

A one-year dog study with a LOAEL of 5 mg/kg/day was considered. However, this study was not selected because the observed effects were considered minimal and the toxicity could have been enhanced due to enterohepatic circulation. This mode of action is species specific of the dog in handling an organic acid and is not

relevant to human exposure.

Incidental Oral Exposure (short- and intermediate-term): Methemoglobinemia is the principal toxicological effect of concern for propanil. This effect was seen at week 13 (the first measurement period) in rats and dogs. Since there are no data for earlier time points this endpoint and dose (9.0 mg/kg/day) observed at week 13 in the rat chronic toxicity/carcinogenicity study was selected for this exposure scenario. An uncertainty factor (UF) of 100 is applied to account for both interspecies extrapolation and intra-species variability. An additional UF of 3 is applied for the use of a LOAEL (total UF = 300).

Dermal Exposure (short/intermediate/long-term): The 21-day dermal toxicity study in rabbits was not selected because methemoglobinemia was not measured in this study, and this effect was seen in three other species (mice, rats, and dogs). As above, the endpoint and dose (9.0 mg/kg/day) observed at week 13 in the rat chronic toxicity/carcinogenicity study was selected for this exposure scenario. An uncertainty factor (UF) of 100 is applied to account for both interspecies extrapolation and intra-species variability. An additional uncertainty factor of 3 is applied for the use of a LOAEL (total UF = 300).

Dermal Absorption: No dermal absorption study is available. An upper-bound dermal absorption estimate (factor) of 20% has been extrapolated based on the maternal LOAEL (100 mg/kg/day) from the developmental toxicity study in rabbits and the LOAEL (500 mg/kg/day) from the 21-day dermal study in rabbits. The ratio is 100/500, or 20%, and this factor is applied to dermal exposure estimates.

Inhalation Exposure (short/intermediate/long-term): Except for an acute inhalation study, which placed propanil in Toxicity Category IV (LC_{50}>6.1 mg/L), no other studies are available for this route of exposure. As above, the endpoint and dose (9.0 mg/kg/day) observed at week 13 in the rat chronic toxicity/carcinogenicity study was selected for this exposure scenario. An uncertainty factor (UF) of 100 is applied to account for both interspecies extrapolation and intra-species variability. An additional UF of 3 is applied for the use of a LOAEL (total UF = 300). An assumption is made that 100% of inhalation exposure is absorbed.

3.4 Carcinogenic Potential

On May 9, 2001, the HED Cancer Assessment Review Committee (CARC) of the Office of Pesticide Programs met and evaluated the carcinogenic potential of propanil. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC classified propanil into the category *"Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential"*. The decision was based on the following

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weight-of-the-evidence considerations: (1) propanil induced testicular interstitial cell adenomas in male rats. The hepatocellular adenomas in female rats occurred *only* at an excessively toxic dose. The increase in commonly occurring malignant lymphomas in female mice added little to the overall weight-of-the-evidence for the carcinogenic potential of propanil. (2) propanil was largely not mutagenic in both *in vitro* and *in vivo* studies. A quantified carcinogenic dose-response assessment (Q_1* approach) is not indicated for propanil.

3.5 Endocrine Disruption

3.5.1 Propanil-Specific Data

In the two generation reproduction study in rats, delayed vaginal perforation and balanopreputial separation was observed in F1 adolescents, and decreased mean testicular sperm count and production rate was noted in F1 adult males. These findings are highly suggestive of neuroendocrine disruption, although hormonal measurements in the two-generation reproduction study did not identify specific alterations in testosterone, luteinizing hormone (LH), or estrodiol levels in F0 males at study termination. Nevertheless, the delays in sexual development are supported by a number of other considerations, including: the presence of treatment-related testicular interstitial cell tumors in the rat chronic toxicity/carcinogenicity study with propanil (often related to neuroendocrine disruptions), and the similarities between the reproductive toxicity profiles of propanil to linuron and flutamide, two structurally-related chemicals with a demonstrated neuroendocrine mode of action affecting the hypothalamic-pituitary-testicular (HPT) axis. [In rat studies, linuron has been shown to 1) delay sexual maturation, 2) cause abnormalities in male reproductive organs and result in alterations to spermatogenesis, and 3) result in significant incidences of Leydig cell tumors after prolonged exposure].

3.5.2 Endocrine Disruptor Screening Program (EDSP)

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) *"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."* Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops

and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, propanil may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Usage Summary

Propanil [3,4-dichloropropionanilide] belongs to the general chemical class of anilides/acetanilides. Propanil is a selective postemergence herbicide registered for use on rice, barley, oats, wheat, and turf to control broadleaf (morningglory, ducksalad, redstem, smartweed, jointvetch, sesbania) and grass (barnyardgrass, sprangletop, crabgrass, goosegrass, foxtail, wiregrass) weeds. Propanil acts primarily in the leaves and is a strong inhibitor of the *Hill reaction* (a light-initiated reaction that splits water resulting in the production of free oxygen). Chlorophyll is an essential ingredient in the reaction, catalyzing the production of oxygen from water and the transfer of the hydrogen to a hydrogen-acceptor.

Propanil is available as an emulsifiable concentrate liquid, a soluble concentrate liquid, a flowable concentrate liquid, and a dry flowable; and is applied as a broadcast treatment by ground and aerial equipment.

For the requirements of reregistration, a profile of past and current propanil usage has been developed by the OPP Biological and Economic Analysis Division (D. Donaldson memo, 2/21/01) based on EPA, USDA/NASS, CAL EPA, and National Center for Food and Agricultural Policy (NCFAP) data. Based on data from 1988 through 1999, an annual estimate of propanil's total domestic usage averaged 9,370,000 pounds active ingredient (a.i.) on a total of 2,527,000 acres treated. The registrant reports that total usage is declining based on an observed decline in the use rate (lbs a.i./acre) and the number of applications per season. It should be noted that, although propanil is registered for use on small grains (barley, duram/spring wheat, oats), more than 99% of actual use is on rice. Also, the Agency estimates that less than one percent of the total acres grown to barley and oats are treated with propanil. Approximately one percent of spring wheat acres are treated, and use on rice ranges from 70 to 88 percent of total acres.

The use of propanil on cereal grains (barley, duram/spring wheat, oats) is restricted to North Dakota, Minnesota, Montana, and South Dakota. A single, post-emergence application is made at a maximum of 1.13 lb a.i./acre (1.5 lb a.i./acre on

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hard red spring wheat). Use after the 4/5 leaf stage is prohibited, as is grazing (the grazing restriction will be rescinded for the small grains). The maximum labeled rate for turf is 10.0 lb a.i./acre.

Use of propanil on rice is limited to the mid-southern region and California. For rice, two applications may be made at a maximum rate of 4.0 lb a.i./acre or a single application may be made at a maximum rate of 6.0 lb a.i./acre. Typical use on rice is at 15 days after planting, followed by flooding the field until 30-45 days post-plant when a second application is made (approximately 90 days before harvest). The registrant(s) report that propanil is applied primarily by air in the mid-southern region (>90%) and primarily by ground in California.

4.2 Dietary Exposure

4.2.1 Tolerance Summary

Tolerances for residues of propanil in/on plant, animal, and processed commodities are established under 40 CFR 180.274 (a)(1) and (a)(2). These tolerances are currently expressed as the combined residues for propanil (3',4'-dichloropropionanilide) and its metabolites (calculated as propanil). The Agency recommends that the propanil tolerance expression for plant and animal commodities be revised to specify that the residues of concern are propanil and its related residues convertible to 3,4-dichloroaniline (3,4-DCA).

Adequate residue data has been submitted to reassess the tolerances for barley, rice, oats, and wheat grain, straw, and associated livestock commodities (meat, milk, eggs). Adequate residue data has been submitted to establish tolerances for crayfish, oat and wheat forage. Residue data is *not* adequate to establish tolerances for barley, oat, and wheat hay. Reassessed tolerance levels range from 0.05 ppm (meat/milk/crayfish) to 75 ppm in rice straw. Reassessed tolerance levels in rice are 10 ppm (grain), 40 ppm (bran), and 30 ppm (hulls). Reassessed tolerances in animal commodities are less than 1 ppm.

The HED Metabolism Assessment Review Committee (MARC) has reviewed the propanil toxicology and metabolism data (meeting dates of 1/16/96 and 8/7/01) and concluded that human health risk assessment should be based on estimates of exposure to propanil (parent), 3,4-dichloroaniline, and related residues convertible to 3,4-dichloroaniline (3,4-DCA).

Similar Compounds: The MARC does not recommend aggregating residues of 3,4-dichloroaniline for the propanil, linuron, and diuron risk assessments. 3,4-dichloroaniline is a significant residue of concern for propanil, but is not a residue of concern *per se* for diuron or linuron. The analytical method for quantifying residues of

concern from diuron and linuron converts all residues to 3,4-dichloroaniline as a *convenience*, but 3,4-dichloroaniline was not a significant residue in any metabolism or hydrolysis study. Therefore, the MARC recommended that all residues convertible to 3,4-dichloroaniline would be included in the tolerance expression for diuron and linuron because no validated enforcement method was available for the quantification of individual components of the residues of concern.

4.2.2 Metabolism in Plants and Animals

The qualitative nature of propanil residue in plants and animals is adequately understood based on submitted metabolism studies in rice, wheat, ruminants, poultry, and crayfish.

Plants: In plants, a majority of propanil residue is present, either as 3,4-dichloroaniline (3,4-DCA) conjugates or incorporated into natural constituents. Uniformly ring-labeled [^{14}C] propanil was foliarly applied to rice plants 23 days after planting at an application rate of 3.0 lbs a.i./A to the soil and 3.0 lbs a.i./A. Residues identified in rice matrices included; propanil *per se*; 3,4-DCA; 3,4-dichloro-glucosylamine; and 3′,4′-dichloroacetanilide. A total of 5% of the grain total radioactive residue (TRR) was identified as radiolabeled glucose thereby demonstrating that in rice, propanil is broken down and incorporated into natural components. Aqueous residues were identified as multicomponent polar moieties, consisting of sugars and conjugates with 3,4-DCA. In wheat straw 4% of the TRR was identified as propanil *per se*, 4% TRR as 3,4-DCA, and 1% as N-(3,4-dichlorophenyl)-glucosylamine. Aqueous metabolites were partially characterized as polar, possibly sugars or conjugates with 3,4-DCA.

Animals: In livestock, significant metabolites such as 3′,4′-dichloro-6′-O-sulfonic acid-acetanilide in ruminant milk and liver, and 3,4-dichloroaniline-N-sulfamic acid in poultry liver, kidney, meat, skin and egg are not convertible to 3,4-DCA, and in turn not quantitated using the enforcement method. However, since these metabolites are in the detoxification pathway, it is likely that the metabolites will be excreted from the body more quickly than propanil or 3,4-DCA. The HED Metabolism Committee concluded that the residue to be regulated in livestock commodities is propanil and residues convertible to 3,4-DCA; there is no need for individual quantitation of propanil metabolites.

Ruminants: Lactating goats were dosed with uniformly ring-labeled [^{14}C] propanil at 53 ppm in the diet for five days. Radioactive residues were solvent-extracted from milk, liver, kidney, fat, and leg and loin muscle. Following extraction and hydrolysis, bound residues in the liver constituted 11% of total radioactive residue (TRR), but bound residues were less than 4% TRR in all other tissues. Propanil, *per se*, was identified in all tissues at 1-6% TRR, but was not found in milk. The principal

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residue identified in liver, muscle and fat was 3′,4′-dichloroacetanilide which constituted 29 - 49% of TRR. The major metabolite in kidney was 3′,4′-dichloroxaloanilide (36% TRR). Principal residues in fat were 3′,4′-dichloroacetanilide (42% TRR) and 3′,4′-dichlorolactanilide (28% TRR). The principal metabolite in milk was tentatively identified as a dimer of propanil, and, although identity of the metabolite was not confirmed, the registrant demonstrated that the metabolite is detected using the enforcement method. Other significant metabolites in milk (not convertible to 3,4-DCA) were 3′,4′-dichloro-6′-O-sulfonic acid-acetanilide (14% TRR) and 2-hydroxy-3′,4′-dichloromalonoanilide (16% TRR).

Poultry: Hens were dosed with uniformly ring-labeled [^{14}C] propanil at approximately 50 ppm in the diet for seven days. The predominant metabolites detected in hen tissues and eggs were 3′,4′-dichloroacetanilide; 3,4-dichloroaniline-N-sulfamic acid; 3′,4′-dichlorolactanilide; 3,4-DCA; and propanil *per se.* Metabolites that constituted greater than 10% of the TRR were 3′,4′-dichloroacetanilide (found in eggs and all tissues except kidney tissue) and 3,4-dichloroaniline-N-sulfamic acid (found in all tissues and egg, except fat). Dichloroaniline was not detected in thigh muscle and fat. Propanil, *per se,* was detected in every tissue except breast muscle. The results of the metabolism study indicate that in poultry, propanil is metabolized to 3′,4′-dichlorolactanilide and then to 3,4-DCA before conjugation with acetyl and sulfate moieties.

4.2.3 Residue Analytical Methods

Adequate residue analytical methods are available for tolerance enforcement and data collection. No additional data pertaining to this guideline topic are required for reregistration.

Plant Matrices: A GC/NPD method (EN-CAS Method No. ENC-9/90) has been submitted by Rohm and Haas. The method has been previously described and deemed adequate for data collection on rice and wheat matrices. It has been subjected to a successful independent laboratory validation (ILV) trial and was adequately radiovalidated using [^{14}C] labeled samples from the confined rotational crop study. Residues are determined as 3,4-DCA, and calculated as the parent, propanil. This method has a limit of quantitation (LOQ) of 0.01 ppm, with a limit of detection of 0.003 ppm.

Animal Tissue: The current preferred enforcement method for milk, eggs, and animal tissue is the GC/ECD method listed in PAM Volume II as Method I. The 8/26/87 Residue Chemistry Chapter reported that hydrolysis procedure used in this method (16 hours reflux distillation in 25% NaOH) has been shown to release ~55-65% of the total [^{14}C]-residues as DCA in milk and eggs. The reported LOQ of Method I is 0.05 ppm. Also, an adequate GC/NPD method was (more recently) used to

analyze samples of eggs, milk, and animal tissues collected from the poultry and ruminant feeding studies. The method (with some modifications) is based on EN-CAS Method No. ENC-9/90, described above for crop matrices. Residues are determined as 3,4-DCA, and calculated as the parent compound. The LOQ for residues of propanil are 0.05 ppm in tissues (liver, kidney, muscle, and fat), 0.01 ppm in eggs, and 0.005 ppm in milk.

Multiresidue Methods: The reregistration requirements for multiresidue method testing for residues of propanil and 3,4-DCA are satisfied. The 10/99 FDA PESTDATA database (PAM Volume I, Appendix I) indicates that propanil is completely recovered (>80%) using multiresidue methods PAM Volume I Sections 302 (Luke method; Protocol D) but is not recovered using Method 303 (Mills, Onley, and Gaither method; Protocol E) and 304 (Mills method for fatty food). There is a *variable* recovery of 3,4-DCA using Method 302 and a *small* recovery (<50%) of 3,4-DCA using Method 303.

4.2.4 Field Trial Data

Tolerance levels and dietary risk assessment are based on field trial data conducted on rice, barley, oats, and wheat. The reregistration requirements for data depicting the magnitude of propanil residues in barley, grain; barley, straw; oat, forage; oat, grain; oat, straw; rice; rice, straw; wheat, forage; wheat, grain; and wheat, straw are fulfilled. Overall, a sufficient number of field trials were conducted, and the trials were conducted using representative propanil formulations at the maximum registered application rates.

Two studies depicting the magnitude of propanil residues in/on rice grain were submitted in response to the data gaps specified in the 8/26/87 Residue Chapter. In field trials conducted in Arkansas, California, Louisiana, and Texas, the 4 lb/gal EC formulation was applied at 4.0 - 8.0 lb a.i./A ($^1/_2$ -1x the maximum registered seasonal rate). Rice grain samples were collected at a 60 - 97 day pre harvest interval (PHI). Propanil residues (determined as base-releasable 3,4-DCA) exceeded the established tolerance of 2 ppm in/on treated rice grain samples, and residues ranged from 0.03 ppm to 8.7 ppm. In another study propanil residues (determined as base-releasable 3,4-DCA) ranged from 0.04 ppm to 2.2 ppm in/on rice grain harvested either 67 to 80 days following the last of two postemergence applications at 4.0 lb a.i./A/application or 56 to 58 days following a single postemergence application at 6.0 lb a.i./A. Based on the available data, the registrant was requested to propose a revised tolerance, from 2 ppm to 10 ppm, for propanil residues in/on rice grain along with the establishment of a 60-day PHI.

4.2.5 Processing Data

Wheat/oats/barley: The requirement for a processing study was waived based

on the early-season application timing (4/5 leaf stage or earlier) and the lack of residues in/on wheat grain (<0.01 ppm) observed in a 5x exaggerated rate field trial study. The Agency does not expect residues to concentrate in the processed products of wheat.

Rice: An acceptable rice processing study demonstrated no concentration of residues in polished rice and average concentration factors of 3.5x for rice hulls and 4.6x for rice bran. Based on the highest average field trial (HAFT) of 8.7 ppm and observed concentration factors, the maximum expected residues are 30.5 ppm for hulls (8.7 x 3.5) and 40.02 ppm for bran (8.7 x 4.6). These expected residues are higher than the reassessed tolerance of 10 ppm for rice grain. Based on these data, the registrants must propose higher tolerances for rice hulls (from 10 ppm to 30 ppm) and rice bran (from 10 ppm to 40 ppm).

4.2.6 Residue Estimates for Risk Assessment

Residue Estimates for Rice/Wheat/Barley/Oats: Past and current use on wheat, barley, and oats is estimated to be less than 1 percent of total propanil usage in the U.S., per year. Rice is the only significant *potential* source of dietary exposure to propanil. The chronic anticipated residue estimate for rice is calculated by averaging field trial residue data (submitted by the registrant to support tolerances) and incorporating the weighted average percent crop treated estimate for rice (70%). Note that field trial data are generally considered to be an upper-bound estimate of actual residue at the time of consumption. Wheat, oats, and barley (also blended commodities) had no reported detections in the field trial data and exposure is taken into account by using half the limit of detection (LOD) and incorporating the percent crop treated estimate of 1 percent.

FDA monitoring data are available for propanil plant commodities, however, the data were determined to be inappropriate for use in this chronic dietary assessment due to the lack of 3,4-DCA samples analyzed, and the multiresidue method used is listed as having variable recovery of 3,4-DCA.

Residue Estimates for Meats/Milk/Eggs: Since barley, oats, rice, and wheat are also used as animal feed commodities, the potential transfer of propanil residues to animal commodities (meat, milk, eggs) must also be accounted for in dietary risk assessment. Metabolism studies have demonstrated a "transfer" of propanil or its metabolites to animal tissue and milk. This aspect of the chronic dietary risk assessment relies on extrapolated residue levels in tissue, milk, and eggs based on an estimate of the possible (average) exposure, or "burden" to livestock from treated items, and residue transfer factors derived from ruminant and poultry feeding studies. Exposure from crayfish is based on tolerance level residue determined by field trial data.

4.2.7 Dietary Risk Estimates

Acute Dietary Exposure / Risk: Acute dietary risk is *not* assessed for propanil based on the conclusion of the HIARC Committee that no appropriate endpoint, attributed to a *single dose* can be identified.

Carcinogenic Risk: Propanil has been classified into the category defined as "*suggestive evidence of carcinogenic potentail by all routes of exposure, but not sufficient to assess human carcinogenic potential*". A quantified carcinogenic risk estimate is not appropriate for propanil.

Chronic Dietary Exposure / Risk: Based on the conclusions of the HED HIARC Committee, dietary risk for propanil is assessed by comparing chronic dietary exposure estimates (in mg/kg/day) to the propanil cPAD. Dietary risk is expressed as a percent of the cPAD. The propanil cPAD is 0.003 mg/kg/day based on a RfD of 0.03 mg/kg/day (see Section 3.3.1, Endpoint Selection Discussion), and incorporating the FQPA safety factor of 10 for all population subgroups.

The cPAD method of risk assessment is applicable to the oral exposure route and is used to assess both food and drinking water exposure. Exposure estimates that are less than 100% of the cPAD indicate a determination of safety can be concluded. The following summarizes the Agency's current method for determining exposure due to use on food commodities.

Chronic dietary risk is estimated for the general U.S. population and population subgroups defined by sex, age, region, and ethnicity. Durations of chronic exposure vary from one-year as represented by infants, to lifetime as represented by the general U.S. population which combines all population subgroups to form a mean exposure value. It should be noted that all parameters of chronic dietary exposure estimates are averaged values (i.e. average food consumption, average residue, etc.). Dietary exposure estimates are also factored by the estimated weighted average usage of propanil, or "percent crop treated" data.

Consumption Data/DEEM Software: Chronic dietary exposure was estimated using the Dietary Exposure Evaluation Model (DEEM™) software which incorporates 1989-1992 consumption data from the USDA's Continuing Surveys of Food Intake by Individuals (CSFII). The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and therefore represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. For chronic exposure assessment, consumption data are averaged for the general U.S. population and within population subgroups. It should also be noted that

the averaged consumption values include "non-users" who reported no consumption of all or particular food items.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., rice-rough or rice-milled) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food-form. The resulting residue x consumption estimate for each food or food-form is summed with the residue x consumption estimates for all other food or food-forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates (Table 4) are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is repeated for each population subgroup.

Table 4. Dietary Risk Estimates

Population	Exposure mg/kg/day	% Chronic PAD
U.S. Population	0.000165	6
All Infants (<1 year)	**0.000379**	**13**
Children 1-6 years	0.000351	12
Children 7-12 years	0.000235	8
Females 13-50 years	0.000129	4
Males 13-19 years	0.000148	5
Males 20+ years	0.000144	5
Seniors 55+ years	0.000105	4

4.3 Drinking Water Exposure

The following information concerning propanil in drinking water is taken from *"Tier 1 Drinking Water Estimated Environmental Concentrations for propanil and its major degradate 3,4- dichloroaniline (3,4-DCA) from use on rice"* (I. Abdel-Saheb memo to R. Griffin, 9/14/01) provided by the Environmental Fate and Effects Division. A decision was made to not address potential drinking water contamination for the small grains due to the very minor usage reported.

4.3.1 Residue Profile

Available data indicates that propanil will not persist in the field. Based on

acceptable studies, propanil is rapidly metabolized under aerobic or anaerobic conditions in a water/sediment milieu (laboratory $t_{1/2}$ = 2-3 days). Acceptable aquatic field dissipation studies in rice paddies at two sites indicate short half-lives for propanil in the water (undetectable after no more than one day) and in the soil (sediment detections were near the quantitation limit, 0.01 ppm, by 2-7 days). The principle metabolic degradate, 3,4-DCA, reached a peak value (2.7 ppm) in soil (sediment) at 1 to 5 days after the second of two applications, remained high for 1 to 2 weeks, and was near detection limits, 0.01 ppm, for 4-6 months. Propanil is susceptible to biodegradation, yet stable to chemical degradative processes. Propanil metabolized rapidly in aerobic soil with a half-life of 0.5 days. However, propanil is stable to hydrolysis at pHs 5, 7, and 9 in the laboratory and, based on marginally acceptable study, propanil is stable to unsensitized aqueous photolysis. A supplemental soil photolysis study also suggests that propanil is stable to photodegradation, and the observed transformation was due mainly to metabolic activity.

The available mobility studies (K_{oc} values) indicate that propanil is in the medium mobility class for sand, sandy loam, and clay loam soils, and has low mobility in silty clay loam and silt loam soils (ASTM, 1996). The partition coefficient (K_d) for propanil ranges from 0.538 (sand) to 11 (clay loam), and K_{oc} values ranged from 306 (sand) to 800 (silt loam), respectively.

Acceptable aquatic field dissipation studies also indicate that propanil and 3,4-DCA are associated generally with the sediment rather than the aqueous phase. Detectable residues are confined largely to the top 2 inches of the sediment.

Based on mobility criteria detailed above (highly soluble, medium K_{oc} and K_d values), propanil could possibly reach groundwater but due to its rapid metabolism in a water/soil matrix, it is not likely to persist for a significant amount of time to leach in significant quantities. The possible exception are sites of extreme vulnerability and low metabolic capacity which would most probably occur only for terrestrial uses. If propanil does reach groundwater in these vulnerable areas, it is expected to be stable [in groundwater].

4.3.2 Surface Water

Monitoring: At the present time, the Agency has limited monitoring data on the concentrations of propanil and 3,4-DCA in surface water. The U.S. Geological Survey (USGS) National Water Quality Assessment Program (NAWQA) reported in its pesticide occurrence and concentrations (database) for 62 agricultural streams (1992-1996) a detection rate for propanil of 2.6% for the 1560 water samples analyzed, with a maximum concentration of 2.05 ppb. A USGS study analyzed 219 water samples collected in Mississippi, Missouri, Tennessee, Arkansas and north Louisiana (mostly creeks, bayous and rivers) from February 1996 to February 2001 (sampling every 2

weeks to one month) and showed that 3,4-DCA did not exceed 8.9 ppb in surface water (49 % detection rate, 68 samples). In south Louisiana, there were three samples reported for 3,4-DCA, with a maximum concentration of 0.06 ppb.

Modeling: The Office of Pesticide Programs currently has no official model for estimating EECs in surface water for rice culture. Therefore a screening calculation method was developed and is *provisional* only. Surface water concentration estimates were modeled for the two major rice growing regions in the United States; California and the mid south (Gulf Coast and Mississippi Valley including parts of northern Louisiana, Mississippi, Arkansas, and southern Missouri. A soil was selected for each region representative of those used for growing rice in that area. The primary way that rice culture causes contamination of surface water with pesticides is through release of the flood water on the paddy. This can occur where precipitation causes overflow of the levee or through the intentional release of the paddy water as part of the agricultural management. The Agency has estimated the concentration of propanil *per se* and 3,4-DCA in rice paddy water at the time of release, as affected by soil metabolism, aquatic metabolism, and through binding to the paddy soil.

Estimated drinking water concentrations are based on the *Index Reservoir* in Shipman, Illinois. This is a 144,000 m^3 reservoir in a 172-hectare watershed. Based on the default Percent Cropped Area (PCA) factor of 0.87, the Agency assumed that there would be a maximum of 150 hectares of rice paddies in the watershed. Also assumed is a release of all 150,000 m^3 of paddy water into the reservoir on day 78 in California (i.e., normal release 90 days from planting), day 28 for the Gulf Coast (simulating a large storm 40 days after planting) and on day 43 in the Mississippi Valley (simulating a normal draining of the paddies).

Estimates from the modeling are higher than the limited existing surface water monitoring data for propanil targeted to the pesticide use area.

4.3.3 Groundwater

Monitoring: EFED has limited monitoring data on the concentrations of propanil in groundwater. Validated monitoring data for propanil for the states of California, Arkansas, Missouri, and Mississippi shows that propanil was detected in two wells out of a total of 124 in Missouri. The range of concentration was 0.06 - 0.07 ppb. The USGS NAWQA program analyzed pesticide occurrence and concentrations for major aquifers and shallow ground water in agricultural areas. Maximum propanil concentration in 933 samples, collected from major aquifers was 0.015 ppb (detection limit = 0.01 ppb). The maximum propanil concentration in 301 samples from shallow groundwater sites was 0.015 ppb, which is higher than that predicted using the SCI-GROW model. Even though the groundwater monitoring data collected by NAWQA are from sites considered as typical use areas, the frequency of sampling and the

length of sampling period were not adequate for regulatory purposes.

Modeling: The SCI-GROW model was used to estimate potential groundwater concentrations. SCI-GROW is a screening model for ground water. It is based on a regression approach which relates the concentrations found in groundwater in Prospective Ground Water studies to aerobic soil metabolism rate and soil-water partitioning properties of the chemical.

Estimates from the SCI-GROW modeling do agree with limited existing groundwater monitoring data for propanil targeted to the pesticide use area.

Table 5. Estimated Environmental Concentrations

Estimated environmental concentrations (ppb) of propanil and 3,4-DCA in surface and groundwater from use on rice.						
Scenario	propanil (ppb)		3,4-DCA (ppb)		use(s) modeled	Percent Cropped Area PCA
	peak	long term average	peak	long term average		
California	0.7	0.02	106	6.2	two applications on rice @ 4 lb ai/acre (1.3 lb ai/acre for 3,4-DCA)	Default PCA (0.87)
Gulf Coast	236	5.9	1007	59		
Mississippi Valley (overflow release)	489	12.2	1022	60		
Mississippi Valley (normal release)	0.65	0.02	118	6.9		
Groundwater/ (peak and long term average	≤.001	≤.001	0.35	0.35		

4.4 Residential Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, groundboom application methods could also be a potential source of exposure. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product

labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

HED has determined that, other than the possibility of spray drift exposure, there are no potential post-application residential or recreational exposures. The turf use is restricted to sod farms only. Although propanil treated sod may eventually be used in residential settings (i.e., residential lawns), propanil residues are not expected to occur at levels that would present a residential post-application risk concern. Since the proposed use of propanil on turf is post-emergent, applied at sod farms early in the turf growing season (well before harvest), HED concludes that the amount of time is adequate to allow residue dissipation to a level that would not cause any significant exposure to residents.

5.0 AGGREGATE EXPOSURE ASSESSMENT

The Agency, as part of the propanil reregistration eligibility decision, is required by the Food Quality Protection Act to ensure *"that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there is reliable information."*

The following aggregate risk assessment uses the dietary exposure estimates completed for propanil food uses to evaluate the estimates of drinking water contamination *modeled* by the Environmental Fate and Effects Division. Aggregate risk for propanil addresses exposure from food and drinking water *only*. Chronic residential exposures to propanil are not expected and, therefore, not included in this aggregate assessment. For propanil, the only interval of exposure to be assessed is chronic (one year or more) and the only route of exposure to be assessed is oral (food and water). Aggregate risk, and related drinking water levels of comparison (DWLOC) estimates have been made in accord with the HED interim guidance (*Updated "Interim Guidance for Incorporating Drinking Water Exposure into Aggregate Risk Assessments,"* 8/1/99).

5.1 Chronic Aggregate Risk / Drinking Water Levels of Comparison

HED uses "drinking water levels of comparison" (DWLOC) values as surrogate measures of exposure. As part of aggregate risk assessment, HED compares the calculated DWLOC to the EEC(s) estimated for surface water and groundwater. If the

DWLOC is greater than the estimated surface and groundwater concentration (i.e., if the DWLOC > EEC) a determination of safety can be made by the Agency for aggregate exposure to a particular pesticide. If the DWLOC values are not greater than the EEC values the Agency may require additional data concerning water contamination.

The following equation was used to calculate the chronic DWLOC value required for propanil aggregate risk assessment:

$$DWLOC_{chronic}\ (\mu g/L) = \frac{[\text{allowable chronic water exposure (mg/kg/day) x (kg body weight)}]}{[\text{consumption (L/day) x } 10^{-3}\ \text{mg}/\mu g]}$$

where allowable chronic water exposure (mg/kg/day) = cPAD (0.003 mg/kg/day) minus estimated chronic food exposure (mg/kg/day). DWLOCs are calculated for males, females, and children (1-6) based on default water consumption estimates of two liters per day for males and females and one liter per day for children.

Chronic Risk Estimates for Food Uses

Population	cPAD (mg/kg/day)	Exposure mg/kg/day	% Chronic PAD
Children (1-6)	0.003	0.000351	12
Females	0.003	0.000129	4
Males	0.003	0.000144	5

Chronic DWLOC Calculations						
Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Chronic Water Exposure (mg/kg/day)	Groundwater EEC (Rice) (μg/L)	Surface Water EEC (Rice) (μg/L) based on propanil *and* 3,4-DCA	DWLOC chronic (μg/L)
Children	0.003	0.000351	0.002649	0.4	Range of: 6 - 72	26
Females	0.003	0.000129	0.002871	0.4	6 - 72	86

Males	0.003	0.000144	0.002856	0.4	6 - 72	100

5.2 Drinking Water Discussion

In general, the EEC estimates for propanil *per se* and 3,4-DCA (combined) are less than the estimated DWLOC; and a conclusion can be drawn (based on the cPAD approach) that no adverse toxicological effect will occur due to aggregate chronic exposure. An immediate conclusion of safety cannot be made for the population subgroup of children (1-6 yrs old) since the DWLOC is less than the upper-end of the estimated range of EECs. However, since the EEC estimates are based on upper-end input parameters (notably the maximum application rate), the assessment does not necessarily indicate a concern for human health, but possibly a need to refine the drinking water exposure estimates. This issue will be considered by the Agency as part of propanil reregistration.

6.0 CUMULATIVE EXPOSURE ASSESSMENT

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this reregistration review for propanil because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with propanil. For purposes of this reregistration decision, EPA has assumed that propanil does not have a common mechanism of toxicity with other substances.

On this basis, the registrant(s) must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether propanil shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for propanil need to be modified or revoked. If HED identifies other substances that

share a common mechanism of toxicity with propanil, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized in 2001.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE ASSESSMENT

Occupational risk is assessed for exposure at the time of application (termed "handler" exposure) and assessed for exposure following application, or postapplication exposure. Handler risk is assessed for mixer/loader, applicators (drivers, pilots, etc.), and flaggers, and is based on both dermal and inhalation exposure. Postapplication risk is assessed for activites such as scouting, irrigating, pruning, and harvesting and is based primarily on dermal exposure estimates. Note that occupational risk estimates are intended to represent professional pesticide workers, and on this basis assumptions are made concerning acres treated per day, and the duration of exposure reflects application to multiple sites. In many scenarios, it is likely that a grower would mix, load, and apply chemicals all in one day because of limited labor, efficiency, or many other reasons. However, for this risk assessment, mixing/loading and applying are considered separate job functions primarily due to a lack of data that allow additivity between tasks to be appropriately assessed.

Scenarios that may be limited in nature, such as flagging during aerial applications, have been evaluated. Engineering controls (i.e., Global Positioning Satellite technology) are now predominantly used as indicated by the 1998 National Agricultural Aviation Association (NAAA) survey of their membership. It appears; however, flaggers are still used in approximately 10 to 15 percent of aerial application operations. Also, it is currently thought that ground-based flagging cannot exceed 350

acres per day unlike the acreage reported for aerial rice application (3,200 acres per day).

Endpoint / Dose Selection for Occupational Risk Assessment: Occupational risk estimates are expressed as margins of exposure, or MOEs which are the ratio of estimated exposure to an established dose level. Propanil margins of exposure are determined by a comparison of specific exposure scenario estimates to the dose level (LOAEL) of 9.0 mg/kg/day observed in the rat chronic toxicity/carcinogenicity study. The Agency has established a "target" margin of exposure of 300 for propanil users based on the standard uncertainty factors of 10x (interspecies extrapolation); 10x (intraspecies variability); and an additional 3x for the lack of a study NOAEL. The dose level selected (9.0 mg/kg/day) applies to exposure durations of "short-term" (1-30 days) and/or "intermediate-term" (one month to several months). Long-term worker exposure is not expected for propanil.

7.1 Usage Summary Relative to Occupational Exposure

There are currently 37 registered end-use products of propanil that are formulated as emulsifiable concentrate liquids, soluble concentrate liquids, water dispersable granules, and flowable concentrates. The maximum application rate on rice is 8.0 lbs a.i./acre, per season, from two 4.0 lb a.i./A applications, or a single 6.0 lb a.i./A application emergency treatment. The *typical* (average) application rate for rice is 3.1 lbs a.i./A per application, with an average of 1.2 applications per season (D. Donaldson memo, 2/21/01). The maximum labeled application rate for turf is 10 lbs a.i./A and the maximum labeled application rate for small grains is 1.14 lbs a.i./A (no information regarding typical rate). The maximum application rates allowed by labels were used in the risk assessments. Typical rates were used as well in order to allow risk managers to make a more informed risk management decision. Average application rates were available from the SMART meeting of 4/17/01 and BEAD's Quantitative Usage Analysis.

Rice Culture / Propanil Application: There are two main rice growing regions in the United States, California and the Mid-South (Arkansas, Louisiana, Mississippi, Missouri, and Texas). In the Mid-South, propanil applications are made primarily by aircraft (greater that 90 percent of the total applied). In California, a majority of the applications are made by ground (approximately 80 percent). Propanil is typically applied post-emergent from March through May (a maximum of two applications) and requires an average temperature of 70° F to be effective. Approximately two weeks following rice planting, propanil is applied to the soil and, two days later, the rice field is flushed (the *temporary* flood). Approximately 21 to 30 days later, another application of propanil is made and the field is then flooded again (the *permanent* flood). The rice field is drained 40 to 60 days later; and approximately 90 days following the permanent flood, the rice is mechanically harvested.

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7.2 Occupational Handler

7.2.1 Exposure Scenario Summary

HED identified five major occupational exposure scenarios based on the types of equipment and techniques that potentially can be used for propanil applications. Based on the general use pattern outlined above, the following occupational exposure scenarios were identified for propanil *handler* risk assessment:

(1a) mixing/loading liquids for aerial application;
(1b) mixing/loading liquids for ground application;
(2a) mixing/loading dry flowable for aerial application;
(2b) mixing/loading dry flowable for ground application;

(3) applying sprays with aerial equipment;
(4) applying liquids with groundboom sprayer; and

(5) flagging sprays for aerial application.

Chemical-specific data to assess the above exposure scenarios were not submitted to the Agency in support of the reregistration of propanil. Instead, exposure estimates for these scenarios are taken from the Pesticide Handlers Exposure Database (PHED) which is used to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available.

7.2.2 Pesticide Handlers Exposure Database

PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts - a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates).

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumption that the magnitude of handler exposures to pesticides are primarily a function of activity (e.g., mixing/loading, applying), formulation type (e.g., wettable

powders, granulars), application method (e.g., aerial, groundboom), and clothing scenarios (e.g., gloves, double layer clothing). Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (e.g., chest upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body.

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments.

7.2.3 Application Estimates

Aerial Application: Total acres of rice treated per day by *aerial* equipment is assessed for mixer/loaders and applicators at 3,200 acres (based on data provided by the Propanil Task Force who also report that application occurs over a 2-3 week interval), at 1,200 acres (the standard HED estimate for rice), and 350 acres per day (the estimated low-end of a range) for approximately 2-3 weeks. Total acres of small grains treated per day by aerial equipment is assessed for mixer/loaders and applicators at 1,200 acres (HED policy) and 350 acres per day (low end of range). Total acres of turf (sod farm) treated per day by aerial equipment is assessed for mixer/loaders and applicators at 350 acres per day. Flaggers are assessed for 350 acres per day for rice, small grains, and turf.

Groundboom Application: Total acres of rice and small grains treated per day by groundboom equipment is assessed for mixer/loaders and applicators at 200 acres (HED policy) and 80 acres per day (low-end of range). Total acres of turf (restricted to sod farms) treated per day by groundboom equipment is assessed for mixer/loaders

and applicators at 80 acres per day.

7.2.4 Standard Factors for Risk Assessment

1) Calculations are completed at the maximum and typical application rates to establish a range of exposure.

2) Average body weight of an adult handler is 70 kg and the workday is assumed to be an average 8 hours.

7.2.5 Handler MOE Estimates

The following table (Table 7) represents occupational handler risk estimates for mixing, loading, applying, and flagging during application of propanil to rice, small grains, and turf. The application rates are based on the maximum and typical (for rice only - 3lbs ai/acre) application rates listed on the propanil labels. The estimated area treated values represents the high end estimate of the area of land that may be treated by a worker on a single day. The total short- and intermediate-term MOE values represent the total MOE (combined dermal and inhalation) for a particular scenario at the following levels of mitigation: (1) baseline: baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, open cab tractor and baseline inhalation unit exposure represents no respirator, (2) minimum PPE: minimum PPE for dermal scenarios include chemical resistant gloves (90% Protection Factor) and minimum PPE for all inhalation scenarios include a dust/mist respirator (5-fold Protection Factor), (3) maximum PPE: maximum PPE for all dermal scenarios includes double layer of clothing (50% Protection Factor for clothing) and chemical resistant gloves (90% Protection Factor) and maximum PPE for all inhalation scenarios include an organic vapor respirator (90% Protection Factor), and (4) engineering controls: engineering controls for mixer/loader include closed mixing/loading, single layer clothing and scenario 1a and 1b also include chemical resistant gloves and engineering controls for applicators and for flaggers include enclosed cockpit, cab or truck, single layer clothing, no gloves.

The target MOE value is 300 and any MOE value less than 300 is considered a risk concern. Once a scenario has exceeded the target MOE no further calculations are necessary and a dash (-) will indicate that the scenario's calculated MOE exceeded the target MOE at a previous level of mitigation (MOE>300). **Bolded** MOEs have a risk concern at the highest possible level of mitigation for corresponding scenarios.

Table 7. Occupational Handler Risk Estimates

Exposure Scenario (Scenario #)	Crop	Application rates[a]	Area Treated	Total Short- and Intermediate-term MOE[b] Baseline[b,f]	Total Short- and Intermediate-term MOE Min PPE[c,f]	Total Short- and Intermediate-term MOE Max PPE[d,f]	Total Short- and Intermediate-term MOE Eng. Control[e,f]
Mixer/Loader							
Mixing/Loading Liquids for Aerial application (1a)	Rice	6 lb ai per acre (maximum application rate)	350 Acres per day	0.5	62	85	**170**
			1200 Acres per day	0.15	18	25	**49**
			3200 Acres per day	0.06	7	9	**18**
		3 lb ai per acre (typical application rate)	350 Acres per day	1	120	170	330
			1200 Acres per day	0.3	36	50	**97**
			3200 Acres per day	0.11	14	19	**36**
	Small Grains	1.14 lb ai per acre	350 Acres per day	2.7	330	--	-
			1200 Acres per day	0.79	95	130	**260**
	Turf	10 lb ai per acre	350 Acres per day	0.31	37	51	**10**
Mixing/Loading Liquids for Groundboom application (1b)	Rice	6 lb ai per acre (maximum application rate)	80 Acres per day	2.3	270	370	-
			200 Acres per day	0.9	110	150	**290**
		3 lb ai per acre (typical application rate)	80 Acres per day	4.5	540	-	-
			200 Acres per day	1.8	220	300	-
	Small Grains	1.14 lb ai per acre	80 Acres per day	12	1400	-	-
			200 Acres **per day**	4.8	570	-	-
	Turf	10 lb ai per acre	**80 Acres per day**	1.4	160	220	440
Dry Flowables for Aerial application (2a)	Rice	6 lb ai per acre (maximum application rate)	350 Acres per day	21	22	32	1100

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Exposure Scenario (Scenario #)	Crop	Application rates[a]	Area Treated	Total Short- and Intermediate-term MOE Baseline[b,f]	Total Short- and Intermediate-term MOE Min PPE[c,f]	Total Short- and Intermediate-term MOE Max PPE[d,f]	Total Short- and Intermediate-term MOE Eng. Control[e,f]
			1200 Acres per day	6.3	6.6	9.2	320
			3200 Acres per day	2.3	2.5	3.5	**120**
		3 lb ai per acre (typical application rate)	350 Acres per day	43.0	45	63	2200
			1200 Acres per day	13.0	13	18	640
			3200 Acres per day	4.7	4.9	6.9	**240**
	Small Grains	1.14 lb ai per acre	350 Acres per day	110	120	170	5700
			1200 Acres per day	33	34	49	1700
Dry Flowables for Groundboom application (2b)	Rice	6 lb ai per acre (maximum application rate)	80 Acres per day	94	98	140	4800
			200 Acres per day	38	39	55	1900
		3 lb ai per acre (typical application rate)	80 Acres per day	190	200	280	9500
			200 Acres per day	75	79	110	3800
	Small Grains	1.14 lb ai per acre	80 Acres per day	490	-	-	-
			200 Acres per day	200	210	290	10,000

Exposure Scenario (Scenario #)	Crop	Application rates[a]	Area Treated	Total Short- and Intermediate-term MOE Baseline[b,f]	Total Short- and Intermediate-term MOE Min PPE[c,f]	Total Short- and Intermediate-term MOE Max PPE[d,f]	Total Short- and Intermediate-term MOE Eng. Control[e,f]
Applicator							
Sprays for Aerial application (3)	Rice	6 lb ai per acre (maximum application rate)	350 Acres per day	see eng. control	see eng. control	see eng. control	**280**
			1200 Acres per day	see eng. control	see eng. control	see eng. control	**82**
			3200 Acres per day	see eng. control	see eng. control	see eng. control	**31**
		3 lb ai per acre (typical application rate)	350 Acres per day	see eng. control	see eng. control	see eng. control	560
			1200 Acres per day	see eng. control	see eng. control	see eng. control	**160**
			3200 Acres per day	see eng. control	see eng. control	see eng. control	**61**
	Small Grains	1.14 lb ai per acre	350 Acres per day	see eng. control	see eng. control	see eng. control	1500
			1200 Acres per day	see eng. control	see eng. control	see eng. control	430
Sprays for Aerial application (3)	Turf	10 lb ai per acre	350 Acres per day	see eng. control	see eng. control	see eng. control	**170**
Sprays for Groundboom application (4)	Rice	6 lb ai per acre (maximum application rate)	80 Acres per day	370	-	-	-
			200 Acres per day	150	180	230	500
		3 lb ai per acre (typical application rate)	80 Acres per day	740.0	-	-	-
			200 Acres per day	300.0	-	-	-
	Small Grains	1.14 lb ai per acre	80 Acres per day	2000	-	-	-
			200 Acres per day	780	-	-	-
	Turf	10 lb ai per acre	80 Acres per day	220	270	350	-

Exposure Scenario (Scenario #)	Crop	Application rates[a]	Area Treated	Total Short- and Intermediate-term MOE[f] Baseline[b,f]	Total Short- and Intermediate-term MOE Min PPE[c,f]	Total Short- and Intermediate-term MOE Max PPE[d,f]	Total Short- and Intermediate-term MOE Eng. Control[e,f]
Flagger							
Flagging for Sprays application (5)	Rice	6 lb ai per acre (maximum application rate)	350 Acres per day	120	140	**150**	5900
		3 lb ai per acre (typical application rate)		240	290	**290**	12000
	Small Grains	1.14 lb ai per acre	350 Acres per day	620	-	-	-
	Turf	10 lb ai per acre	**350 Acres** per day	71	87	**88**	**3500**

Footnotes:

a Application Rates are based on the maximum application rates listed on the Propanil labels.

b Baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, open cab tractor and baseline inhalation unit exposure represents no respirator[8].

c Minimum PPE for all dermal scenarios include chemical resistant gloves (90% Protection Factor) and minimum PPE for all inhalation scenarios include a dust/mist respirator (5-fold Protection Factor).

d Maximum PPE for all dermal scenarios include double layer of clothing (50% Protection Factor for clothing) and chemical resistant gloves (90% Protection Factor) and maximum PPE for all inhalation scenarios include an organic vapor respirator (90% Protection Factor).

e Engineering Controls for mixer/loader include closed mixing/loading, single layer clothing and scenario 1a and 1b also include chemical resistant gloves. Engineering Controls for applicators and flaggers include enclosed cockpit, cab or truck, single layer clothing, no gloves.

f Total MOE (combined dermal and inhalation) = 1 / ((1/dermal MOE) + (1/inhalation MOE))
where: Short-and Intermediate term dermal MOE = Short-and Intermediate term NOAEL (9 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
and Short- and Intermediate-term inhalation MOE = Short- and Intermediate-term NOAEL (9 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).

The target MOE value is 300.
Scenario's calculated MOE exceeds the target MOE at the previous level of mitigation (MOE>300)
Bolded MOEs have a risk concern at the highest possible level of mitigation for corresponding scenarios

7.2.6 Summary of Risk Concerns for Handlers

Propanil labels prohibit application by chemigation. Most current propanil labels have the following PPE requirements for handlers: long sleeve shirt, long pants, waterproof gloves, shoes, socks, protective eye wear. Some labels have additional PPE requirements of chemical resistant headgear for overhead exposure. Other labels state only that eye and skin protection should be worn when handling and entering treated areas before they have dried.

The above short- and intermediate-term dermal and inhalation MOE estimates were combined based on their having the same endpoint. MOE estimates were calculated for all scenarios at baseline, minimum PPE, maximum PPE, and engineering control level exposures. Due to lack of data, a 98% protection factor was applied to the baseline unit exposure values to determine the unit exposure for the engineering control level of protection for the dry flowable scenarios.

MOEs that **meet or exceed** the target MOE of 300 at the *baseline* level are the following; 1) scenario (2b) - mixing/loading dry flowable for groundboom application to small grains; 2) scenario (4) - applying sprays, using a groundboom, to rice at 80 acres per day, and to small grains at 80 and 200 acres per day; and 3) scenario (5) - flagging for sprays applications on small grains.

MOEs that **meet or exceed** the target MOE of 300 at the *minimum PPE* level are the following; 1) scenario (1a) - mixing/loading liquids for aerial application to small grains at 350 acres per day; 2) scenario (1b) - mixing/ loading liquids for groundboom application to rice at 80 acres per day, and to small grains at 80 and 200 acres per day; and 3) scenario (4) - applying sprays with a groundboom to turf at 80 acres per day.

MOEs that **meet or exceed** the target MOE of 300 at the *engineering control* level are the following; scenario (1b) - mixing/loading liquids for groundboom application to turf at 80 acres per day; scenario (3) - applying sprays by aerial equipment to small grains at 350 and 1,200 acres per day; scenario (4) - applying sprays with a groundboom to rice at 200 acres per day; and scenario (5) - flagging for spray application to rice and turf.

Calculations of risk based on dermal and inhalation exposure indicate that the combined dermal and inhalation margins of exposure (MOEs) are **less than** the target MOE of 300 with *maximum risk reduction measures* for the following short- and intermediate-term occupational exposure scenarios listed: scenario (1a) mixing/ loading liquids for aerial application to rice at 350, 1200, and 3200 acres at 6 lbs a.i./acre, scenario (1a) mixing/loading liquids for aerial application to rice at 1200 and 3200 acres at 3 lbs a.i./acre, scenario (1a) mixing/loading liquids for aerial application

to small grains at 1200 acres at 1.14 lbs a.i./acre, scenario (1a) mixing/loading liquids for aerial application to turf at 350 acres at 10 lbs a.i./acre, scenario (1b) mixing/loading liquids for groundboom application to rice at 200 acres at 6 lbs a.i./acre, scenario (2a) mixing/loading dry flowable for aerial application to rice at 3200 acres at 6 lbs a.i./acre, scenario (2a) mixing/loading dry flowable for aerial application to rice at 3200 acres at 3 lbs ai/acre, scenario (3) applying sprays, using aerial application to rice at 350, 1200, and 3200 acres at 6 lbs a.i./acre, and scenario (3) applying sprays, using aerial application to turf at 350 acres at 10 lbs a.i./acre.

7.3 Occupational Postapplication

Workers can be exposed to propanil residues by entering previously treated areas to perform certain agricultural activities. Exposure varies with specific tasks, the level of propanil residue in the environment, and the duration of the activity. The Agency is concerned about postapplication exposure to two types workers; crop advisors (scouts), and all others (hoers, irrigators, etc.). Postapplication risks are mitigated for workers, such as hoers, using a restricted-entry interval (REI). In general, the REI is established based on the number of days following application that must elapse before the pesticide residues dissipate to a level where estimated worker MOE's equal or exceed 300 while wearing baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks). Under the Worker Protection Standard for Agricultural Pesticides (WPS) -- 40 CFR Part 170, entry to perform routine hand labor tasks is prohibited during the REI and personal protective equipment can not be considered as a risk reduction measure in establishing the REI. Postapplication risks are mitigated for crop advisors/scouts using entry restrictions, not restricted-entry intervals. Since under the Worker Protection Standard for Agricultural Pesticides -- 40 CFR Part 170, crop advisors/scouts are defined as handlers, the Agency can permit such persons to enter treated areas to perform scouting tasks, provided they are using required personal protective equipment.

7.3.1 The Worker Protection Standard

The Worker Protection Standard (WPS) restricted-entry intervals (REIs) for agricultural workers are based on the acute dermal toxicity and skin and eye irritation potential of the active ingredient. For propanil, the acute dermal toxicity is toxicity category III, primary skin irritation is toxicity category IV, and primary eye irritation is toxicity category II. An REI of 24 hours was established for propanil based on the primary eye irritation toxicity category.

The WPS prohibits routine entry to perform hand labor tasks during the REI and requires PPE to be worn for other early-entry tasks that require contact with treated surfaces. Most of the propanil labels specify the following early entry PPE: long sleeve shirts, long pants, waterproof gloves, shoes, socks, and protective eye wear. A

few labels also specify chemical resistant footwear and chemical resistant headgear for overhead exposure.

7.3.2 Postapplication Exposure Estimates

Although the Worker Protection Standard provides a basic level of of protection for pesticide workers, the reregistration process reexamines, by the MOE approach, the required restricted-entry intervals and entry restrictions to determine the intervals necessary for protection. Lacking propanil-specific data relating to postapplication exposure, a surrogate-type of assessment has been made. In general, a surrogate-type re-entry exposure assessment is quantified by estimating the amount of residue available (dislodgeable foliar residue and/or turf transferrrable residue) for uptake, and by estimating the rate of uptake for specific activities by using "transfer coefficients".

Transfer coefficients used in this assessment for rice and small grains (barley and spring wheat) are from the Agricultural Reentry Task Force (ARTF) database. An interim transfer coefficient policy was developed by HED's Science Advisory Council for Exposure using the ARTF database. It is the intention of HED's Science Advisory Council for Exposure that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from the further analysis of studies already submitted to the Agency, and from the studies in the published scientific literature.

The rice and small grain surrogate assessments use the lower transfer coefficient of 100 cm^2/hr associated with minimal foliage development based on propanil's early season use (application to rice approximately 14 and 35-40 days after planting with harvest at 120 -140 days and in small grains before the five- leaf stage). The sod/turf farm surrogate assessment used a low transfer coefficient of 500 cm^2/hr for the activities of aerating, fertilizing, mowing, and scouting and a high transfer coefficient of 16,500 cm^2/hr for the activities of transplanting and weeding.

No propanil-specific dislodgeable foliar residue (DFR) or turf transferable residue (TTR) data exist. Instead, the DFR estimate is based on an estimate of 20 percent of the rate applied as initial dislodgeable residue for rice and small grains, and 5 percent of the rate applied as initial turf transferable residue for turf. A dissipation rate of 10% per day is estimated for rice, small grains, and turf.

Table 8. Postapplication Summary

Crop	Maximum Label Application Rate (lbs ai/acre) [a]	Transfer Coefficient [b] (cm^2/hr)	Activity [c]	DAT [d]	DFR [e] ($\mu g/cm^2$)	MOE [f]
Rice	6 (maximum application rate)	100	Scouting minimum foliage development.	0 (12 hours)	13.45	**293**
				1	12.11	325
	3 (typical application rate)	100	Scouting minimum foliage development.	0 (12 hours)	6.72	585
Small Grains	1.14	100	Irrigation and scouting minimum foliage development.	0 (12 hours)	2.56	1541
Turf	10	16500	Transplanting and hand weeding.	0 (12 hours)	22.42	**12**
				18	0.84	312
		500	Aerating , fertilizing, hand pruning, scouting, mechanically weeding, hand/mechanically harvesting.	0 (12 hours)	5.60	703

Footnotes:

[a] Maximum application rates as stated on current propanil labels.

[b] Transfer Coefficients from Science Advisory Council on Exposure Policy 3.1.

[c] Activities from Science Advisory Council on Exposure Policy 3.1. Every activity listed may not occur for every crop in the group.

[d] DAT is "days after treatment"

[e] Initial DFR ($\mu g/cm^2$) = Application rate (lbs ai/A) x Conversion factor (1 lb ai/acre= 11.209 $\mu g/cm2$) x Fraction of initial ai retained on foliage (20% for small grains and rice and 5% for turf)

[f] MOE = NOAEL (mg/kg/day) / Dermal dose (mg/kg/day). Target MOE = 300.

The estimated MOE for rice (at the maximum application rate) exceeds the target MOE of 300 one day after application for scouting in (minimal foliage development based on early season use). The estimated MOE for rice (at a typical application rate) is greater than the target MOE on the day of application for scouting (minimal foliage development). The estimated MOE for small grains (at a typical application rate) exceeds the target MOE on the day of application for scouting (minimal foliage development). The calculated MOE for sod farms is greater than 300 on the day of application for activities such as mowing, scouting, mechanical weeding, and irrigation and 18 days after application for activities such as hand and mechanical harvesting, transplanting, and hand weeding.

7.4 Human Incident Data Review

The following data bases have been consulted for the poisoning incident data on the active ingredient propanil:

OPP Incident Data System (IDS): Reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested. A pesticide incident occurred in 1997, when a twenty-one year old female reported nausea, muscle weakness, respiratory problems, and a skin rash less than 24 hours after spraying the product to clean out some weeds. This exposure involved a mixture of propanil and MCPA. A review of the exposure circumstances led the registrant's toxicologist to conclude that the reported symptoms were not related to the exposure. No further information on the disposition of the case was reported. A pesticide incident occurred in 1997, when a sixteen year old child was exposed to the product and reported eye irritation and pain and respiratory irritation. No further information on the disposition of the case was reported.

Poison Control Centers: As the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1998 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc. Results for the years 1993 through 1998 were acquired for 8 exposures to propanil reported to Poison Control Centers. Cases involving exposures to multiple products are excluded. Only one case was reported among children under six years of age and two cases among older children and adults exposed at their workplace. There were 5 non-occupationally exposed cases among older children and adults. This was too few cases to warrant detailed analysis. Half of the cases did not develop any symptoms as a result of their exposure or in 1 case was not expected to develop symptoms. None of these cases reported a major outcome, though one exposure was considered potentially toxic, and one case reported a moderate outcome. Only 1 of all 8 cases was reported to have been seen in a health care facility.

California Department of Pesticide Regulation: California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by

statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided. Detailed descriptions of 2 cases submitted to the California Pesticide Illness Surveillance Program (1982-1999) were reviewed. In the first case, the worker applied the product by hand and reported a skin rash. In the second case, the worker applied the product by hand and reported chest pain and heart burn. The worker was diagnosed with gastritis. In both of these cases the relationship between exposure and health effects was considered possible.

National Pesticide Telecommunications Network (NPTN): NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others. On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, propanil was not reported to be involved in human incidents.

Literature Review: DeSilva and Bodinayake (1997) reported on five patients that ingested propanil and were treated at a hospital. The first patient died after intensive treatment for haemolysis. The second patient reported acute hepatitis requiring a transfusion and treatment with methylene blue. The third, fourth, and fifth patient reported a mild poisoning and were treated with methylene blue. All of the patients were diagnosed with methemoglobinemia. Estimated dose for all five male adults was around 100-200 ml of a 36% solution of propanil.

Yamazaki et al. (2001) reported on a forty-seven year old male who ingested propanil and carbaryl mixture. He reported methemoglobinemia and lung congestion and edema and later died. His blood cholinesterase level was within the antemortem normal range. Propanil was considered "most probably responsible for the death". Estimated dose was at least 10 ml and half of the 100 ml bottle at the scene was empty and reported to contain 25% propanil and 5% carbaryl.

Morse et al.(1979) reported on a health effects evaluation in August 1976 at a plant that manufactured methomyl and propanil in rural Arkansas. The plant employed about 111 workers. Of these workers, 102 participated in the study. Ninety-six percent of the workers were male and 88% were white. Their average age was 28.7 years and worked at the plant for about 24 months. A questionnaire was administered to the workers that covered demographics, work history, symptoms or history of chemical poisoning, personal habits, and sources of other chemical exposure. Production workers (28) exposed to dichloroaniline and propanil had symptoms of chloracne (61%), blueness (cyanosis 21%), and skin rash (46%). An

acetylcholinesterase test was conducted that showed no significant depression in the workers surveyed. The study concluded that the occurrence of chloracne in production workers was caused by dichloroaniline and propanil exposure. However, it should be noted that at that time (the report is dated 1979) propanil was reported to be contaminated a level much higher (up to 14% of technical product) than the trace level of contamination currently reported.

8.0 DATA NEEDS / LABEL REVISIONS

Although the database for propanil is considered adequate for risk assessment, data deficiencies have been identified. Also, HED is recommending several immediate label revisions.

8.1 Toxicology

Studies required by the Agency include: 1) developmental neurotoxicity; 2) 28-day inhalation toxicity; 3) 30-day oral study in rats with methemoglobin measurements at days 1, 5, 7, 14, 21, and 30; and 4) a guideline immunotoxicity study (or a literature search to better characterize its immunotoxic potential.

8.2 Residue Chemistry

Wheat hay data are required for propanil reregistration.

Additional data for irrigation and potable water *may be* required for reregistration of propanil if the registrant is not willing to establish a 7-day retreatment interval for rice and a 30-day discharge interval for water in treated paddies following application of propanil to rice paddies.

The Pesticide Analytical Manual (PAM) Volume II lists a colorimetric method (designated Method II) for determination of propanil residues in/on rice matrices, eggs, milk, and animal tissues. The Agency no longer considers this colorimetric method to be suitable for enforcing propanil tolerances; however, the method EN-CAS Method No. ENC-9/90, with some modifications, has been deemed adequate to analyze samples of eggs, milk, and animal tissues. The Agency recommends that the registrant propose method EN-CAS Method No. ENC-9/90 with some modifications for tolerance enforcement method. The method should be radiovalidated and subjected to an Independent Laboratory Validation (ILV) trial in accordance with PR Notice 98/7. To ensure that EN-CAS Analytical Method No. ENC-9/90 for tolerance enforcement on rice and wheat matrices is adequate, it will be forwarded to the Analytical Chemistry Branch for Agency validation.

Revision of product labels with use claims on rice should specify a 60-day PHI

for grain.

Product labels with use claims on barley, oats, and wheat should be modified to delete the feeding restrictions for the grazing of treated chop or cutting for green chop.

All labels with use directions on rice should be amended to specify restrictions against application to fields where catfish farming is practiced and draining water from treated fields into areas where catfish farming is practiced.

All registered propanil labels should be revised to specify a 60-day plant-back interval for all rotational crops.